

Nephrotoxicity rates related to colistin and evaluation of risk factors

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ABSTRACT

Objectives: Colistimethate sodium (colistin) is the member of polymyxins, the cyclic structured cationic polypeptide antibiotics. The purpose of our study is to determine the patients' nephrotoxicity rates and risk factors related to nephrotoxicity development that are under colistin treatment in the tertiary intensive care unit (ICU).

Methods: One-hundred colistin received patients files were reviewed retrospectively, who were in tertiary ICU in Bursa Yüksek İhtisas Training and Research Hospital. Fifteen patients with the history of renal failure were excluded from the study. The data before the first colistin treatment was taken into consideration for the patients received repetitive colistin treatment. RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) classification was used for the evaluation of nephrotoxicity.

Results: The patients mean age was 67.81 ± 16.56 years (range: 21-94) and 52.9% were male. Nephrotoxicity was determined in 35 (41.2%) patients. According to the RIFLE classification the nephrotoxicity rates were determined for risk, injury and deficiency were 24.7%, 10.6% and 5.9%, respectively. Nephrotoxicity was detected in 9 (25.7%) out of 35 patients on the first day of the colistin treatment. Mortality rate was observed as 82.9% in patients with nephrotoxicity.

Conclusions: Colistin treatment is preferable for the treatment of multi drug resistant infections in intensive care unit. The patients, under certain circumstances, i.e., malignancy, using additional nephrotoxic agent and elder age must be closely monitored for the possible nephrotoxicity development.

Keywords: colistin, nephrotoxicity, RIFLE score

Colistimethate sodium (colistin) is a member of the cyclic structured cationic polypeptide antibiotics, polymyxins. The polymyxins which are discovered in 1947, were used for the treatment of the gram-negative bacterial infections since 1962 [1, 2]. Colistin use was decreased gradually, because of its nephro-

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toxicity and several new antibiotics with gram negative effects were taken a place since 1980s. The increase of multiple drug resistant gram negative bacterial infections brings the colistin treatment back to the agenda.

The nephrotoxicity during the colistin treatment is dose dependent and reversible. The increase of colistin concentration by tubular reabsorption and proximal tubular injury is held responsible for the nephrotoxicity. Nephrotoxicity is a serious contraindication to quit the treatment [3, 4].

The purpose of our study is to determine the patient's nephrotoxicity rates and risk factors related to nephrotoxicity development who are under colistin treatment in the tertiary intensive care unit (ICU).

METHODS

Patients older than 18 years who received at least 24-hour colistin treatment in Bursa Yüksek İhtisas Training and Research Hospital's tertiary ICU were enrolled to this study. Six patients with acute renal failure and 9 patients with chronic renal failure were excluded from the study. The patient's data were reviewed from their medical records and ICU follow-up forms, retrospectively. The patients' diagnose, demographic data (age and sex), additional diseases, the existence of malignancy, type of infection, detected microorganisms, duration of hospitalization, APACHE2 (Acute Physiology and Chronic Health Evaluation) scores at the first day of the colistin treatment and daily creatinine values, the need

Table 1. Demographic and clinical features of the patients

Patients features	All patients mean ± SD or n (%)	Nephrotoxicity developed patients mean ± SD or n (%)	Nephrotoxicity not developed patients mean ± SD or n (%)	p value
Demographic features				
Age (year)	67.81 ± 16.56	69.94 ± 16.56	66.32 ± 17.40	0.48
Sex (male/female)	45/40 (52.9/47.1)	20/15 (57.1/42.9)	25/25 (50/50)	0.51
Additional diseases				
Neurologic disease	44 (51.8)	15 (42.9)	29 (58)	0.16
Cardiac disease	35 (41.2)	10 (28.6)	25 (50)	0.65
COPD	19 (22.4)	8 (22.9)	11 (22)	0.92
Hypertension	18 (21.2)	7 (20)	11 (22)	0.82
Diabetes mellitus	13 (15.3)	7 (20)	6 (12)	0.16
Malignancy	6 (7.1)	5 (14.3)	1 (2)	0.03
Need of positive inotrop	62 (72.9)	29 (82.9)	33 (66)	0.08
Mortality	59 (69.4)	29 (82.9)	30 (60)	0.02
APACHE II score				
In the acceptance to intensive care unit	23.16 ± 5.24	22.94 ± 5.20	23.33 ± 5.34	0.75
In the first day of the colistin treatment	24.54 ± 6.87	24.64 ± 6.65	24.48 ± 7.10	0.80

COPD = Chronic obstructive pulmanory disease, APACHE = Acute Physiology and Chronic Health Evaluation

for hemodialysis and inotrope therapy during the treatment were all recorded. The data before the first colistin treatment was taken into consideration for the patients received repetitive colistin treatment. Concurrently used drugs, like; carbapenem, glycopeptide, vancomycin, aminoglycoside and diuretics were noted. RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) classification was used for nephrotoxicity evaluation.

Statistical Analysis

Chi-square analysis was used for evaluation of categorical variables. The t-test or corresponding non-parametric test was used for analysis of continuous variables. A *p* < 0.05 value was accepted as statistically significant for all analyses.

RESULTS

Eighty-five patients were included to the study. Sixty-eight of them have additional diseases and 6 patients have malignancy. Demographic and clinical features of the patients were given on the Table 1.

Nephrotoxicity developed in thirty-six (41.2 %) patients. According to the RIFLE criteria risk, injury and failure rates were found as 24.7%, 10.6%, 5.9%, respectively (Table-2). Nephrotoxicity was developed in 9 (25.7%) patients on the first day of the treatment. Twenty-two (62.9 %) patients developed nephrotoxicity in the first week. Mortality rates after colistin treatment was determined as 82.9% in the nephrotoxicity developed group and 60% in the others,

Table 2. The nephrotoxicity rates according to the RIFLE score

Criteria	Number of patients (%)
No risk	50 (58.8)
Risk	21 (24.7)
Injury	9 (10.6)
Failure	5 (5.9)
Total	85 (100)

RIFLE = Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease

the difference were statistically significant (*p* = 0.02).

When assessed for accompanying diseases, 51.8% of the patients had neurological disease and 41.2% had cardiac disease. Nephrotoxicity rate was 40.3% in patients with accompanying disease and 44.4% in patients without accompanying disease (*p* = 0.75).

Nephrotoxicity rate (83.3%) was significantly higher in patients with malignancy than in those without malignancy (*p* = 0.03). Concomitant use of aminoglycoside, glycopeptide, vancomycin, carbapenem and diuretic was higher in the group with nephrotoxicity (Table 3). Although, the need for inotropic agent higher in nephrotoxicity developing group (46.8 vs. 26.1%), it was not statistically significant (*p* = 0.08). Hemodialysis is required in 17.1% of the patients who has nephrotoxicity.

The number of patients treated with colistin for pneumonia, bacteremia, wound infection, urinary

Table 3. The relationship between concurrent drug use and development of nephrotoxicity

Concurrent use of drug	All patients n (%)	Nephrotoxicity developed patients; n (%)	Nephrotoxicity non developed patients n (%)	<i>p</i> value
Diuretic	56 (65.9)	26 (74.3)	30 (60.0)	0.17
Carbapenem	52 (61.2)	22 (62.9)	30 (60.0)	0.79
Vancomycin	11 (12.9)	6 (17.1)	5 (10.0)	0.44
Glycopeptide	10 (11.8)	3 (8.6)	7 (17.0)	0.33
Quinolon	9 (10.6)	2 (5.7)	7 (14.0)	0.22
Aminoglycoside	2 (2.4)	1 (2.9)	1 (2.0)	0.79

system infection and catheter related infections are 60, 17, 5, 1 and 1, respectively. *Acinetobacter baumannii* (72.9%), *Pseudomonas aeruginosa* (14.1%) and *Klebsiella spp.* (7.6%) were isolated most frequently.

DISCUSSION

The use of colistin is currently recommended only in infections caused by gram-negative microorganisms with multiple drug resistance and particularly in the presence of antibiotic resistance except colistin. For this purpose, it can be used especially for hospital-acquired pneumonia, bacteremia, surgical site infections, catheter infections and urinary system infections caused by resistant gram-negative bacteria, as well as in the treatment of patients with cystic fibrosis and in the treatment of *P. aeruginosa* infections in transplantation patients [1, 2]. In our study, we observed that it is most commonly used for the treatment of patients with pneumonia caused by *Acinetobacter baumannii*.

The nephrotoxicity development rate in patients treated with colistin in ICU has been reported to be 10-50% [3-8]. The different rates of nephrotoxicity in the researches may be related with using different renal failure diagnosis criteria. Today, RIFLE criteria are preferred in acute renal failure (ARF) classification [9]. In our study, we observe nephrotoxicity rates 41.2% rates with using RIFLE criteria in accordance with the literature [6-8].

Nephrotoxicity time was not determined throughout the studies. It has been reported that nephrotoxicity generally developed within the first five to seven days in the majority of nephrotoxicity time given studies [8, 10, 11]. In our study, nephrotoxicity was detected in 25.7% of the patients on the first day of treatment and in 62.9% of patients within the first seven days of colistin treatment, in accordance with the literature.

Cytotoxic agents, nephrotoxic drugs, risk of sepsis or organ infiltration may cause renal injury, but direct renal infiltration of malignancy may also result in ARF [12-14]. Darmon *et al.* [14] reported that the rate of ARF development was 12-49% in patients with malignancy and followed up in ICU. Hachem *et al.* [15] found that 23% of patients with malignant disease developed nephrotoxicity as a result of the use of colistin in the treatment of *pseudomonas* infections.

The rate of nephrotoxicity was significantly higher in patients with malignancy in our study ($p = 0.03$). This data is consistent with other studies [16, 17].

In many studies, elder age, addition of drugs such as vancomycin, aminoglycoside, carbapenem, diuretic and non-steroidal anti-inflammatory drugs, the use and duration of colistin usage has been reported as the risk factors for the development of colistin nephrotoxicity [3, 18-20]. In our study, nephrotoxicity was found to be more common with the age, aminoglycoside, diuretic, carbapenem, glycopeptide and vancomycin simultaneous use, but the difference was not statistically significant.

In our study mortality rate was significantly higher in the nephrotoxicity developed group parallel to some other studies in the literature ($p = 0.02$) [16, 21, 22]. The inotropic need was found to be higher in the nephrotoxicity-developing group, but the difference was not statistically significant ($p = 0.08$). Kaya *et al.* [16], found that the inotropic requirement was higher in the group with nephrotoxicity. Studies evaluating inotropic need in the literature are insufficient and we think that our findings are important for the contribution to the literature.

Limitations

Limitations of our study; single centered, retrospective study and the number of patients is small. There is a need for prospective studies with large patient group.

CONCLUSION

In conclusion, colistin treatment can be preferred for the treatment of the multiple resistant pathogens in ICU patients but during the treatment of elderly patients, malignancy, additional nephrotoxic agent must be followed up closely especially in the first day and first week for the development of nephrotoxicity.

Conflict of interest

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