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Original Article

Risk Factors for Colistin-Associated Acute Kidney Injury: A Multicenter Study from Turkey

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SUMMARY: The aim of this study was to investigate the incidence of acute kidney injury (AKI) and risk factors due to colistin use in patients infected with multidrug-resistant pathogens. This multicenter, retrospective, observational study was conducted in Turkey, at 5 different research and university hospitals. Cox regression analyses were performed, to determine independent predictors of AKI. From April 2012 to July 2014, a total of 216 patients aged between 18–94 years, treated with colistimethate sodium (CMS) were included in the study. The mean age of the patients was 60.3 ± 20.1 years. The overall incidence of AKI was 34.3% (74/216) at any time during treatment. Concomitant use of loop diuretics, baseline creatinine level, and CMS dosage were independently associated with AKI. According to our results, patients with higher baseline creatinine levels, or patients who had to use concomitant loop diuretics may need to be monitored more closely, and dose adjustment should be done promptly. More comprehensive studies are, however, still needed to evaluate the efficacy of low-dose colistin since higher doses tend to increase the risk of AKI.

INTRODUCTION

Colistin, which belongs to the polymyxin class of cationic polypeptide antibiotics, is an old antibiotic that was used until the early 1980s. Owing to its toxicity, colistin has not been used to treat infections caused by Gram-negative bacilli for many years. However, the emergence of multidrug-resistant isolates of Gram-negative bacilli, such as *Acinetobacter baumannii* or *Pseudomonas aeruginosa* has renewed interest in this old drug for its activity against such multidrug-resistant pathogens (1). Renal toxicity is the most common adverse effect of colistin. The mechanism of renal toxicity is not exactly clear, but proximal tubulopathy and mammalian uroepithelium toxicity were observed in some studies. It has been reported that the nephrotoxicity of colistin is generally mild and reversible (2–6).

Nevertheless, little is known about the incidence of renal toxicity and the factors that may enhance nephrotoxicity due to colistin use. We therefore investigated the incidence of acute kidney injury (AKI) and its risk factors due to colistin usage in patients infected with multidrug-resistant pathogens.

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MATERIALS AND METHODS

This multicenter, retrospective, observational study was conducted in Turkey, at the following 5 different research and/or university hospitals:

(i) Kirikkale University Hospital (KUH), a 200-bed tertiary care hospital located in the Middle Anatolia region. (ii) Tokat Gaziosmanpasa University Hospital (GOPUH), a 400-bed tertiary care hospital located in the Middle Black Sea region. (iii) Diyarbakir Dicle University Hospital (DUH), an 1,150-bed tertiary care hospital located in the South-East Anatolia region. (iv) Zonguldak Bulent Ecevit University Hospital (BEUH), a 527-bed tertiary care hospital located in the West Black Sea region. (v) Adana Numune Educational and Research Hospital (NERH), a 910-bed tertiary care hospital located in the Mediterranean region.

From April 2012 to July 2014, patients who were aged ≥18 and who were being treated with colistimethate sodium (CMS) were included in the study. Exclusion criteria were: being <18 years of age, receiving CMS for <72 hours, renal impairment at the beginning of therapy (baseline creatinine level >1.5 mg (for both males and females), and the development of AKI within 24 h of starting CMS treatment.

The demographic and clinical characteristics of patients, daily dosage of CMS (with or without loading dosage), dosage intervals, duration of treatment, comorbid diseases, infection sites, causative bacteria, concomitant nephrotoxic drugs (antibiotics, NSAIDs, loop diuretics) that were received at least within 48 h, and baseline and serial serum creatinine levels were also recorded.

The baseline serum creatinine level was defined as the lowest creatinine value recorded in the 3 days prior to CMS therapy (7).

AKI was assessed according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, as follows: increase in serum creatinine by 0.3 mg/dL developing over 48 h, or >50% developing over 7 days, or urine output of <0.5 mL/kg/h for more than 6 h (8).

The patients were treated with CMS (Colimycin®, Kocak Farma, Turkey; each vial contained 150 mg colistin base activity, which is approximately equivalent to 360 mg, or 5 million IU of CMS), which is the only available form of colistin in Turkey (9–11). Although the prospectus recommendation of IV dosages for CMS is 2.5–5 mg/kg/day (base activity), divided into 2–4 doses for normal renal function, it is usually administered in fixed doses equivalent to 300 mg or 450 mg/day, divided into 2 or 3 doses per day, according to the manufacturer's recommendations in Turkey. Our patients received appropriate dosages in line with this recommendation. Manufacturers who had not previously recommended a loading dose for the drug have recently started to do so. Since some of the patients were enrolled in the study prior to the implementation of this recommendation, these patients were not administered a loading dose for this reason.

Types of infections were assessed according to the US Centers for Disease Control and Prevention (CDC) criteria (12).

Statistical analysis was performed using the SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA). Age, sex, baseline creatinine level, intensive care unit admission, comorbidities, usage of concomitant nephrotoxic drugs, daily dose of base colistin, and infusion time were screened as univariate predictors. Univariate analysis to identify variables associated with AKI due to colistin therapy was performed with the Chi-square, Fisher's exact, Student's t and Mann-Whitney U tests. The tests were selected on the basis of Kolmogorov–Smirnov normality testing with Lilliefors' correction. The possible predictive factors ($P < 0.20$) identified in univariate analysis were further entered into Cox-regression analyses models with forward stepwise selection, to determine independent predictors of AKI. Among correlated factors with similar influence on AKI, only those with clinical significance were included. A 5% type-I error level was used to imply statistical significance.

RESULTS

During the study period, a total of 216 patients (137 males [63.4%] and 79 females [36.6%]) fulfilled the inclusion criteria. The mean age of the patients was 60.3 ± 20.1, ranging between 18–94 years. There was a statistical difference ($P < 0.001$) in the mean ages of the female (66.8 ± 18.5 years) and male (56.5 ± 20.1 years) patients.

Of the 216 patients, 80 (37.04%) were from BEUH, 40 (18.52%) were from DUH, 38 (17.59%) were from NERH, 31 (14.35%) were from GOPUH, and the remaining 27 (12.50%) were from KUH.

The most frequently isolated pathogen in the study patients was *A. baumannii* (91.7%), and nosocomial pneumonia was the most common infection. The other infection sites are shown in Table 1.

The overall incidence of AKI was 34.30% (74/216) at any time during treatment. The median duration from the beginning of CMS therapy to the development of AKI was 5 days (Inter Quartile Range: 3–9 days; range 1–26 days). There were no patients in whom colistin treatment was discontinued due to toxicity. Dose adjustments were appropriately managed and none of the patients needed hemodialysis.

In univariate analysis (Table 2), the mean age of the patients who developed AKI during the colistin treatment was significantly higher than the patients who did not develop AKI (64.6 ± 19.4 vs. 58.0 ± 20.1, $P = 0.021$). AKI developed more commonly in females (Odds Ratio [OR]: 0.54; Confidence Interval [CI]: 0.30–0.97; $P = 0.039$). The development of AKI was also more common among the patients who used concomitant loop diuretics ($P < 0.001$). The incidence of AKI was significantly higher among the patients who were treated with a daily dose of 450 mg CMS (46/95 [48.42%]) when compared to those who were given daily dose of 300 mg CMS (28/121 [23.14%]) ($P < 0.001$).

The initial mean baseline creatinine levels of the patients who developed AKI during the colistin treatment (0.79 ± 0.30) were significantly higher than the patients who did not develop AKI (0.70 ± 0.26).

We were able to observe effects of the loading doses on the development of AKI only in patients who had received 300 mg daily doses of CMS, since not all of them received a loading dose, in contrast to those patients who were treated with 450 mg daily doses of CMS. The manufacturer recommended administering the 450 mg daily dose and the loading dose concurrently. Among those who received a loading dose, the incidence of AKI was 51.72% (15/29), whereas among the patients who did not receive a loading dose the incidence was 14.13% (13/92) and this difference was statistically significant ($P < 0.001$).

Results of the Cox regression analysis (Table 3) indicated that concomitant usage of loop diuretics, baseline creatinine level, and CMS dosage were independently associated with AKI.

Table 1. Site of infections and isolated microorganisms

Variable	Acute kidney injury (n = 74)	Non-acute kidney injury (n = 142)
	Total no. (%)	Total no. (%)
Microorganism		
Acinetobacter	65 (87.8)	127 (89.4)
Pseudomonas	5 (6.8)	6 (4.2)
Acinetobacter + *Pseudomonas*	4 (5.4)	2 (1.4)
Enterobacter	0	2 (1.4)
Klebsiella	0	2 (1.4)
Empirical treatment	0	3 (2.1)
Site of Infection		
Respiratory tract	52 (70.3)	104 (73.2)
Bloodstream	7 (9.5)	14 (9.9)
Urinary tract	3 (4.1)	7 (4.9)
Skin and soft tissue	12 (16.2)	16 (11.3)
Bone and joint	0	1 (0.7)

Table 2. Demographic characteristics and comorbid medical conditions of patients treated with colistin, stratified by whether or not they developed acute kidney injury (n = 216)

Variable	Acute kidney injury (n = 74)	Non-acute kidney injury (n = 142)	P-value	Odds ratio (95% CI)
	Total no. (%)	Total no. (%)		
Age (yr) (mean ± SD)	64.6 ± 19.4	58.0 ± 20.1	0.021	—
Male	40 (54.1)	97 (68.3)	0.039	0.54 (0.30–0.97)
Baseline creatinine (mg/dL) (mean ± SD)	0.79 ± 0.30	0.70 ± 0.26	0.021	—
Intensive care unit (ICU)				
ICU patients	69 (93.2)	119 (83.8)	0.05	2.66 (0.96–7.33)
Non-ICU patients	5 (6.8)	23 (16.2)		
Comorbidities				
Hypertension	16 (21.6)	32 (22.5)	0.87	0.98 (0.48–1.87)
Diabetes mellitus	17 (23.0)	30 (21.1)	0.75	1.11 (0.56–2.18)
Congestive heart failure	5 (6.8)	11 (7.7)	0.79	0.86 (0.28–2.58)
Other nephrotoxic drugs				
Glycopeptides	6 (8.1)	5 (3.5)	0.19	2.41 (0.71–8.2)
Loop diuretics	17 (23.0)	5 (3.5)	<0.001	8.17 (8.17–23.21)
Amphotericin B	1 (1.4)	2 (1.4)	0.97	0.95 (0.0–10.75)
NSAID	18 (24.3)	29 (20.4)	0.51	1.25 (0.64–2.44)
Dose (base colistin)				
300 mg daily	28 (23.1)	93 (76.9)	<0.001	0.32 (0.17–0.57)
450 mg daily	46 (48.4)	49 (51.6)		
Infusion time				
30 min	19 (25.7)	51 (35.9)	0.12	0.61 (0.33–1.15)
60 min	55 (74.3)	91 (64.1)		

Table 3. Results of Cox regression analysis, showing predictors of acute kidney injury

Risk factor	Coefficient (β)	Standard error	Wald test	Hazard ratio (95% CI)	P-value
Loop diuretics	1.03	0.29	12.24	2.80 (1.57–4.98)	<0.001
Baseline creatinine	1.47	0.38	14.71	4.34 (2.05–9.21)	<0.001
Dose (450 mg/day vs. 300 mg/day)	0.83	0.25	10.41	2.31 (1.38–3.84)	0.001

DISCUSSION

CMS can be used as a last therapeutic option since promising new antibiotics have not as yet been developed for multidrug-resistant Gram-negative bacteria. Due to the effectiveness of CMS, particularly to *A. baumannii*, *P. aeruginosa*, and carbapenemase-producing strains, its usage has significantly re-emerged in recent years. However, 1 major concern revolving the usage of CMS is nephrotoxicity.

The rates of colistin-induced AKI reported in the literature vary between 11% and 53.5% (3,4,6,9,10, 13–17). This variability could be attributed to the dose and duration of the therapies, and to the varying definitions of AKI. The overall incidence of AKI in patients treated with CMS was 34.3% in our study.

Although colistin has been used for more than 50 years, the levels of the most effective and least toxic doses are still unclear (18). One reason may be the different dosage recommendations included with various forms of colistin products.

In a majority of published studies, a statistically significant relationship has been observed between the duration and dosage of colistin and the development of AKI (10,17,19), although in some studies this relationship has not observed (20,21). A higher total daily dosage of CMS was found to be an independent risk factor for the development of AKI in our study.

In some earlier studies, a loading dose is recommended for rapidly achieving therapeutic concentrations (22,23). However, data regarding the effects of the loading dose on nephrotoxicity are limited. In our study, the loading dose was shown to increase the risk of AKI development.

In some studies, concomitant NSAID or vancomycin use, hypertension, and older age were identified as independent risk factors for colistin-induced AKI (6,14, 24,25), whereas these findings were not corroborated in several other studies, including ours (10,13,17,19,25, 26).

An association between the use of diuretics and the development of AKI has been shown in previous studies (18,27). Similarly, in our study, concomitant usage of loop diuretics and higher dose colistin were identified as independent risk factors for AKI development.

Kwon et al. (13) identified male sex as an independent risk factor for AKI in patients receiving colistin. However, in many other studies, male sex has not been found to be a significant risk factor (10,17,18,26). In our study, female sex was identified as a risk factor for the development of AKI in univariate analyses. This discrepancy could be attributed to the difference in the mean age between the male and female patients in our study. On the other hand, this risk factor was not ob-

served in Cox regression analysis.

In studies investigating the relationship between the baseline creatinine level and the risk of AKI in postoperative cases, some found that baseline creatinine level is an independent risk factor for developing AKI. (28,29). Our study similarly showed that a higher baseline creatinine level is an independent risk factor for AKI.

In the present study, ICU stay was found to be a risk factor for developing AKI in univariate analysis ($P = 0.05$). This may be due to the higher occurrence of comorbidities and increased use of nephrotoxic drugs in ICU patients. Nevertheless, in Cox regression analyses, ICU stay was not found to be an independent risk factor.

A retrospective design and lack of a control group were the main limitations of our study.

In conclusion, higher baseline creatinine levels, concomitant usage of loop diuretics, and higher total daily dosages of CMS were found to be independent risk factors for AKI.

Patients with higher baseline creatinine levels or patients who have to use concomitant loop diuretics should be monitored more closely, and dose adjustment according to serum creatinine levels should be done promptly. Additionally, more specific randomized clinical trials, taking into account the cohort differences and monitoring plasma colistin levels, may help curtail the use of higher doses of CMS, which can increase the risk of AKI.

Conflict of interest None to declare.

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