Medical Science and Discovery
ISSN: 2148-6832

The Colistin-Related Nephrotoxicity and Risk Factors In The Intensive Care Unit; A Retrospective Study

Guler Eraslan Doganay[1]*, Mustafa Ozgur Cirik[1], Ali Alagoz[1]

1 University of Health Sciences, Atatürk Chest Diseases and Chest Surgery Training and Research Hospital Dept of Anesthesiology and Reanimation, Ankara, TR
*** Corresponding Author:** Guler Eraslan Doganay **E-mail:** gulerdoganay@hotmail.com.tr

ABSTRACT

Objective: Colistimethate sodium (CMS) which is salvage therapy in the management of infections caused by multi-drug resistance (MDR) gram-negative pathogens is eliminated by the kidneys and cause nephrotoxicity. Many factors may also contribute to this nephrotoxic effect. In this study we aimed to determine the risks for the development of nephrotoxicity patients who received CMS in the intensive care unit (ICU).

Materials and Methods: We evaluated retrospectively of the patients who have lung cancer or COPD, aged older than 18 years, and received intravenous CMS therapy at least 72 hours in ICU. Patients' age, comorbidities, C-reactive protein (CRP), procalcitonin, albumin, glomerular filtration rate (GFR), creatinine values on the 1st and 7th days of CMS treatment, positive inotropes, and nephrotoxic drugs used concurrently with CMS therapy, and renal replacement therapy (RRT) were recorded. RIFLE score , lenght of stay (LOS) in hospital and in the ICU, and 28-day mortality were also recorded.

Results: In this study, the GFR and creatinine level deteriorated significantly on the 7th day with CMS therapy patients who had preexisting lower GFR, hypoalbuminemia, and concomitant nephrotoxic drugs usage. The incidence of acute kidney injury was higher in malignant patients and 28-day mortality increased in patients with nephrotoxicity.

Conclusion: The CMS therapy with preexisting lower GFR, hypoalbuminemia, and concomitant nephrotoxic drugs usage significant risk factors to develop nephrotoxicity. It was also higher in malignant patients and increased 28-day mortality. Detailed clinical and laboratory evaluation of the patients is needed before CMS treatment.

Keywords: colistimethate sodium, nephrotoxicity, ICU, risk, mortality

Received 22-10-2020

Accepted 29-12-2020

Published 30-01-2021

INTRODUCTION

Colistin is an antibiotic belonging to the polymyxin group, which as salvage therapy in the management of infections caused by multi-drug resistance (MDR) gram-negative pathogens including Pseudomonas, Acinetobacter, Klebsiella, and Enterobacter species (1, 3). Due to the side effect of nephrotoxicity, its use was abandoned in the last quarter of the 20th century, but with the increase in infections due to multi-resistant gram-negative bacteria in the last two decades, it has been reintroduced due to the lack of a more reliable alternative (1, 4, 5). There are two commercial forms of colistin, colistin sulfate and colistimethate sodium (CMS). Colistin sulfate is eliminated by the extrarenal system, but CMS is eliminated by the kidneys. It is thought that the nephrotoxicity mechanism of CMS increases the cytoplasmic membrane permeability in proximal tubule cells, causing an excessive amount of water to pass into the cell and destroying the cell (6). Hypoalbuminemia, positive inotropes or nephrotoxic drugs use may also contribute to this nephrotoxic effect (7, 8). In clinical practice, CMS is often used as combination therapy, but data on whether combination therapy is superior to monotherapy is limited (9).

http://dx.doi.org/10.36472/msd.v8i1.433

This study aims to determine the risks for the development of nephrotoxicity according to the RIFLE (risk, injury, failure, loss, end-stage kidney disease) criteria by retrospectively evaluating patients using CMS in intensive care unit (ICU) on malignancy and Chronic Obstructive Pulmonary Disease (COPD) patients (Table 1).

Table 1: Definition of RIFLE criteria (9).

Category	Criteria
Risk (R)	Increased creatinine level x 1.5 or GFR decrease >25%
Injury (I)	Increased creatinine level x 2 or GFR decrease >50%
Failure (F)	Increased creatinine level x 3, GFR decrease >75%, or creatinine level >4 mg/dL
Loss (L)	Persistent acute renal failure or complete loss of function for >4 weeks
ESKD (E)	End-stage Kidney Disease for >3 months

GFR:Glomerular Filtration Rate

MATERIALS AND METHODS

After obtaining the approval of the ethics committee (04/07/2019/634) a retrospective review of patients aged ⩾ 18 years who received intravenous CMS therapy for at least 72 hours while under treatment in the ICU January 2018 through December 2018. Patients who were pregnant or breastfeeding, patients receiving concurrent inhaler colistin therapy, patients receiving colistin therapy for less than 72 hours, receiving RRT before starting CMS treatment, and patients with chronic kidney disease were excluded from the study. Demographic data of patients who had COPD or lung cancer, comorbidities as Charlson Comorbidity Index (CCI), C-reactive protein (CRP), procalcitonin, albumin values, glomerular filtration rate (GFR), and creatinine values on the 1st and 7th days of CMS treatment, positive inotropes and nephrotoxic drugs (nonsteroidal anti-inflammatory drugs (NSAID), radiocontrast agents, diuretics, aminoglycoside, vancomycin, anticandidal) used concurrently with CMS therapy, and renal replacement therapy (RRT) was recorded retrospectively. RIFLE score (Table 1), lenght of stay (LOS) in hospital and in ICU, and 28-day mortality were also recorded. CMS therapy was started intravenously 300 mg loading dose and after maintenance dose was administered 5 mg/kg/day (twice-daily dosing regimen) at least 72 hours. Of the 39 patients who received CMS therapy, 2 patients were excluded from the study because one patient had a history of chronic kidney disease, was receiving RRT before starting CMS treatment and one patient died at the 48th hour of therapy. The study was planned with 37 patients (Figure 1).

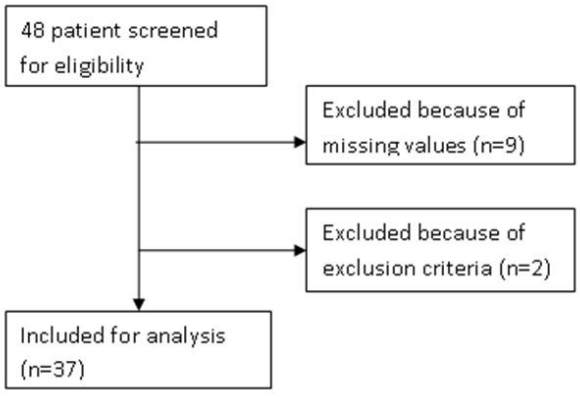

Figure 1: Flow diagram of the subjects.

Statistical analysis: Data analyses were performed by using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, United States). Whether the distribution of continuous variables were normal or not was determined by Kolmogorov Smirnov test. Levene test was used for the evaluation of homogeneity of variances. Unless specified otherwise, continuous data were described as mean ± standard deviation for normal distributions, and median (minimum and maximum value) for skewed distributions.

Categorical data were described as the number of cases (%). Statistical analysis differences in normally distributed variables between two independent groups were compared by Student's t-test, Mann Whitney U test was applied for comparisons of the not normally distributed data. Categorical variables were compared using Pearson's chi-square test or fisher's exact test. It was accepted p-value < 0.05 as a significant level on all statistical analyses.

Logistic regression(LR) analysis was performed for age, APACHE II scores, SOFA scores, CRP levels, procalcitonin levels, albumin levels, concomitant use of positive inotropes and other nephrotoxic drugs, LOS in the ICU and hospital, which were considered as risk factors for acute kidney injury (AKI). The backward LR method was chosen as the method.

First of all, the patients were included in the multivariate analysis to investigate whether the age, albumin levels, concomittant use of positive inotropic drugs , concomitant use of other nephrotoxic drugs, LOS in hospital and in ICU if predictor of nephrotoxicity.

RESULTS

Data of 37 patients who met the inclusion criteria were analyzed. The 24 (65%) of them were male and 13 (35%) were female. Nephrotoxicity developed in 10 (27%) patients, 1 (2.7%) female and 9 (24.3%) male, after using CMS for at least 72 hours in ICU. There was no significant difference in terms of mean age, gender, APACHE II, CCI scores, CRP, and procalcitonin values (p > 0.05). The LOS in the hospital and in the ICU among the patient was not statistically significant groups with and without nephrotoxicity (p > 0.05). The patients' demographic and clinical characteristics are presented in table 2. In the group with nephrotoxicity; while albumin levels (p= 0.021) and GFR values in the 1st day (p= 0.028) of CMS treatment were statistically significantly lower than the group without nephrotoxicity, SOFA scores were higher (p= 0.008). On the 7th day of CMS use, creatinine(p= 0.001) values were statistically significantly higher and GFR values (p= 0.003) were statistically significantly lower in patients with nephrotoxicity compared to patients without nephrotoxicity. The 28-day mortality rate was also statistically significantly higher in patients with nephrotoxicity compared to patients without nephrotoxicity (p= 0.002), but there was no significant difference between the LOS in the hospital and in the ICU(p> 0.05). There was no statistically significant difference regarding the occurrence of nephrotoxicity in terms of concomitant positive inotropes use (p> 0.05). Using the Backward LR method, it was evaluated that in the last 5th step, hypoalbuminemia and the use of concomitant other nephrotoxic drugs were predictive for the development of nephrotoxicity.

http://dx.doi.org/10.36472/msd.v8i1.433

The risk of developing nephrotoxicity is higher in patients with hypoalbuminemia (p= 0.012) and the use of concomitant nephrotoxic drugs (p= 0.026), (Table 3).

ROC curve analysis was performed to determine the effect of albumin level on the development of nephrotoxicity and to determine the cut-off value. When the area under the curve was analyzed, it was determined that it was not statistically significant. (p>0,05), (Table 4), (Figure 2).

Malignancy (p= 0.035) was statistically significantly higher in patients with nephrotoxicity compared to patients without nephrotoxicity.

There were no statistically significant difference in the rates of Chronic Obstructive Pulmonary Disease(COPD) patients (p> 0.05) according to the development of nephrotoxicity (Table 5).

Table 2: Demographic and Clinical characteristic values of patients

	NEPHROTOXICITY				p
	Nephrotoxicity(+) (n:10)		Nephrotoxicity(-) (n:27)		
Age(year)	66.60	± 13.13	70.30	± 13.40	0.459
APACHE II	22.70	± 9.46	19.81	± 6.25	0.287
LOS in Hospital	35.80	± 10.02	38.26	± 25.17	0.767
LOS in ICU	10	(1-34)	8	(1-50)	0.775
Gender Male(n/%)	9	(90.0)	15	(55.6)	0.051
Female(n/%)	1	(10.0)	12	(44.4)	
Albumin(g/l)	2.55	± 0.72	3.05	± 0.50	**0.021**
1st day GFR(ml/min/1.73m^2)	95.5	(67-129)	91	(10-117)	**0.216**
1st day Creatinine(mg/dl)	0.6	(0.4-1.2)	0.8	(0.3-4.9)	0.139
7th day Creatinine(mg/dl)	1.95	(1.2-5.5)	0.9	(0.5-3.3)	**0.001**
7th day GFR(ml/min/1.73m^2)	30.5	(10-66)	81	(13-112)	**0.003**
CCI	6.00	± 3.02	5.33	± 1.90	0.427
Procalcitonin(ng/ml)	0.50	(0.14-9.7)	0.53	(0.01-14.5)	0.533
CRP(mg/l)	13.75	(1.1-23.1)	5.1	(0.1-34)	0.148
SOFA	7.5	(5-17)	5	(4-8)	**0.008**
Nephrotoxic drug					
Anticandidal(n/%)	1	(10.0)	-		
Vancomycin(n/%)	1	(10.0)	1	(3.7)	
Positive inotropes(n/%)	2	(20.0)	4	(14.8)	0.999
28-day mortality(n/%)	9	(90.0)	8	(29.6)	**0.002**
RRT (n/%)	2	(18.2)	-		0.068

Table 3: Variable excluded from multivariate analysis

	B	SE	Wald	P	Exp(B)	95% CI for Exp(B)
Albumin	2.340	0.932	6.299	**0.012**	0.096	(0.015-0.599)
Nephrotoxic drugs	3.484	1.560	4.987	**0.026**	32.581	(1.531-693.145)

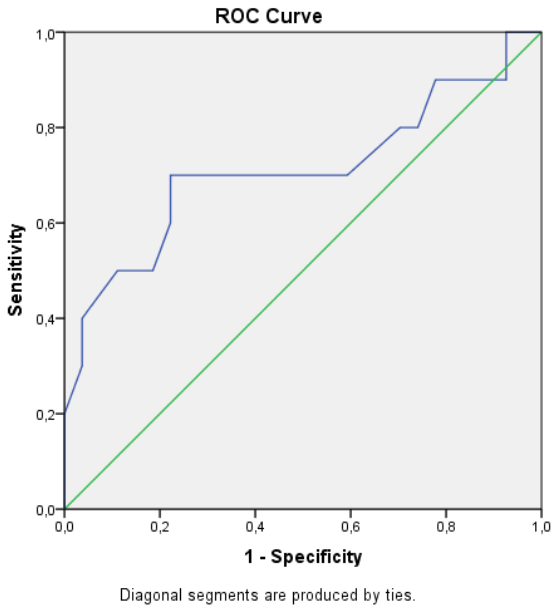

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Table 4: ROC Analysis for albumin results

Area	Std. Error	p	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.711	0.112	0.051	0.492	0.931

Table 5: Effects of COPD and Malignancy on Nephrotoxicity

	Nephrotoxicity(+) (n:10)	Nephrotoxicity(-) (n:27)	p
Malignancy	4 (40)	2 (7.4)	**0.035**
COPD	7 (70)	22 (81.5)	0.655

DISCUSSION

This study shown that hypoalbuminemia, CMS treatment, higher SOFA scores, and simultaneously the use of other nephrotoxic drugs were predictive for the development of nephrotoxicity. CMS treatment causes GFR and creatinine levels impairment approximately in 7 days and the development of nephrotoxicity is higher in patients who have lung cancer.

Nosocomial infections caused by MDR gram-negative microorganisms are an important cause of morbidity and mortality in ICU (10, 11). Due to the side effect of nephrotoxicity (approximately 5-55%) (12) its use was abandoned, but with the increase in infections due to MDR gram-negative bacteria, colistin has been reintroduced due to the lack of a more reliable alternative (1-5). Colistin nephrotoxicity generally develops in the first week of treatment (1).

In this study, we determine the risks for the development of nephrotoxicity according to the RIFLE (risk, injury, failure, loss, end-stage kidney disease) criteria by retrospectively evaluating multi-parameter of patients using colistin in ICU.

In different studies, risk factors for nephrotoxicity include advanced age, pre-existing chronic renal disease, hypoalbuminemia, and the combined use of NSAIDs or vancomycin (1). Similarly, in some studies, among the reasons that increase the risk of acute renal failure due to CMS, male gender, advanced age, diabetes mellitus, obesity, hypoalbuminemia, use of nephrotoxic drugs (13, 14). In our study, in support of these publications, low albumin, low GFR at the beginning of the CMS therapy, simultaneous nephrotoxic drugs use and high SOFA scores increase the development of nephrotoxicity, but no difference was found in terms of comorbidity, advanced age, and gender. Although some risk factors are different from the studies mentioned, many risk factors are related to the development of nephrotoxicity as in our study. If CMS is used as an alternative therapy in MDR gram-negative bacteria, optimizing risk factors as much as possible and close monitoring may limit the development of nephrotoxicity.

It is thought that the nephrotoxicity mechanism of CMS increases the cytoplasmic membrane permeability in proximal tubule cells, causing an excessive amount of water to pass into the cell and destroying the cell (6).

Besides the pathophysiological mechanism of nephrotoxicity, the development of nephrotoxicity in a wide range (12) and ongoing discussions regarding the duration of treatment (1) may be due to the effect of nephrotoxic drugs and other risk factors used during colistin therapy.

Correlation between duration of colistin therapy and nephrotoxicity is controversial. Several studies have examined the dose-dependence of iv colistin-induced nephrotoxicity (15, 16). Some studies suggest that toxicity is related to the total dose and duration of therapy and the total cumulative dose (17, 18). Hartzell, et al found that, while the use of additional nephrotoxic drugs did not affect the development of colistin-related nephrotoxicity, the duration of colistin use was more than 14 days increased the risk of nephrotoxicity four times, and it was increased when this period was exceeded (19). On the contrary, Falagas, et al emphasizes that the duration of colistin therapy did not affect the nephrotoxicity (20).

In some studies older age, prolonged colistin administration, hypoalbuminemia, high CCI, and the presence of septic shock were reported to be related to nephrotoxicity (8, 13, 15, 16, 21). Similarly, a few studies older age, hypoalbunemia, and use of nephrotoxic drugs were identified as significant risk factors (22, 23).

In our study, we examined those who developed nephrotoxicity by looking at GFR and creatinine values on the 1st and 7th days of colistin therapy. We used at least 72 hours as a criterion, but it was not among our data on treatment time in our study; we analyzed 28-day mortality rates, the LOS in ICU and hospital. According to our study findings, 28-day mortality was significantly higher in patients with nephrotoxicity, while the effect of the LOS in ICU and hospital was insignificant.

In the literature, there is a publication that indicates to the development of nephrotoxicity in malignant patients is significantly higher (23). In our study, supporting this situation, patients who developed nephrotoxicity were more likely to be malignant than those who did not but we did not encounter any significant difference in the COPD patients.

We have several limitations for our study. First of all this study is retrospective, there is no control group in our study. In addition, it is a single-center study.

CONCLUSION

The risk of nephrotoxicity increases significantly in patients with hypoalbuminemia and use of concomitant nephrotoxic drugs and on the 7th day of colistin use, deterioration of GFR and creatinine is significant. The incidence of AKI is higher in malignant patients and 28-day mortality increases in patients with nephrotoxicity. For the early detection and prevention of colistin-induced nephrotoxicity with the elimination of possible risk factors crucial for the duration of colistin therapy. Larger-scale and prospective controlled studies are needed to determine possible risk factors and prevention of AKI during the colistin therapy.

Author Contributions: GED, MOC, AA: Project design, Review of the literature, Data collection and statistical analyzes **GED:** Writing and Revisions

Conflict of interest: No actual or potential conflicts of interest exist in relation to this article.

Ethical issues: All authors declare originality of research.

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