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Original Article

Evaluation of colistin-associated acute renal failure in intensive care unit

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Abstract

Aim: Colistin's parenteral use was limited due to nephrotoxicity related to decreased renal perfusion, nephrotoxins and ischemia-reperfusion injury. Colistin became popular again because of multiple drug resistance.
This study aimed to retrospectively evaluate the characteristics of intensive care patient groups with and without colistin-induced acute kidney injury.
Material and Methods: Following approval of local ethics committee, information of the patients, who were treated in the anesthesia and surgical intensive care units between 01/01/2016 and 30/06/2017, were analyzed retrospectively.
Results: Twenty patients (59%) developed acute kidney injury during colistin treatment. No statistically significant difference was observed between the groups with and without acute kidney injury in terms of age, gender and duration of stay in the intensive care unit, however, patients with acute kidney injury were found to be older and stayed in the intensive care unit for a longer period of time. The comparison made between the groups in terms of inotropic agent use showed that the duration of inotropic agent use was statistically longer in the acute kidney injury group.
Discussion: Rate of colistin-induced acute kidney injury varies between 5-55%. In addition, fluid balance of patients is important in acute kidney injury development. Fluid therapy, hourly urine output and central venous pressure trends of the patients should be closely monitored particularly when nephrotoxic medicines are used.
There is a need for large-scale studies with more advanced methodologies for the early detection and prevention of colistin-induced nephrotoxicity.

Keywords: Colistin; Intensive Care; Acute Renal Failure.

INTRODUCTION

Colistin is a cationic polypeptide antibiotic included in the polymyxins. The drug, which is effective against Gram-negative bacteria such as Acinetobacter baumannii (A. baumannii), Pseudomonas aeruginosa (P. aeruginosa), and Klebsiella pneumonia (K. pneumonia), was first introduced in the 1940s and used until the 1980s, however, its parenteral use was limited due to nephrotoxicity. However, colistin has been come to the fore again because of multiple drug resistance and treatment difficulties (1,2). Although the mechanism of nephrotoxicity, which is the most common side effect of colistin, is not fully known, there are cases with proximal tubular and uroepithelium toxicity in the literature. Furthermore, there are also studies showing that nephrotoxicity increases with age (3,4).

Colistin is also known as Polymixin E. Polymyxins consist of five groups from A to E. Of these, polymyxin B and E are used for treatment. There are two different forms of colistin which are colistin sulfate and colistimethate sodium. Colistimethate sodium is inactive until sodium is hydrolyzed, which may be hydrolyzed in in vitro and in vivo environments. This is the reason why colistimethate sodium is about four or eight times less active agent. Colistimethate sodium has less therapeutic efficacy and less side effects than colistin sulfate. It has further less nephrotoxic effect compared to colistin sulfate and polymyxin B (5,6).

Acute kidney injury (AKI) may occur due to decreased renal perfusion, exogenous and endogenous nephrotoxins, ischemia-reperfusion injury (IRI), inflammation and oxidative stress. Kidney Disease Improving Global Outcomes (KDIGO) criteria have been used as the diagnostic criteria for AKI since 2012 (7).

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The aim of this study is to retrospectively evaluate the patient groups with and without colistin-induced AKI among the patients treated in the intensive care unit (ICU).

MATERIAL and METHODS

This study included patients who were staying in the Anesthesiology and Reanimation ICU of Recep Tayyip Erdoğan University Medical Faculty Training and Research Hospital between 01/01/2016 and 30/06/2017 and who developed and did not developed AKI while receiving combined therapy of 300 mg i.v. and/or 75 mg inhaler colistin. These patients were examined retrospectively following the receipt of the local ethics committee approval (06.01.2017 decision no: 1)

Patients without renal failure at the age range of 18-85 years were included in the study. Patients whose colistin dose was changed during treatment and patients with impaired renal function at the time of admission were excluded from the study.

Information about the patients was reached by scanning the patient files and daily ICU follow-up forms. Data on the diagnosis, reasons for admission to ICU, age, gender, duration of stay in ICU, and active microorganism of the patients were recorded. Mechanical ventilation requirements, blood-blood products they received, and inotropic agent requirements were noted. The following information related to the patients who were found to use colistin were recorded: ICU stay, start date of colistin use, values after 48 hours, post colistin treatment, renal function tests (blood urea nitrogen [BUN] and creatinine values), albumin values, hemodialysis needs, and result of treatment (service/death).

Comorbid diseases, additional treatments, diet properties, vancomycin, aminoglycoside, carbapenem, and diuretic use were recorded. KDIGO criteria were used for the evaluation of nephrotoxicity.

According to KDIGO criteria; AKI is defined as any of the following: increase in serum creatine by x0.3 mg/dL or more within 48 hours, increase in serum baseline creatine to x1.5 times within the prior seven days, or urine volume of <0.5 mL/kg/h for six hours (7).

In statistical analysis, student-t test and Chi-square test were was used to compare continuous data and categorical data, respectively. A p value of <0.05 was considered statistically significant.

RESULTS

Colistin treatment was initiated for a total of 40 patients staying in our ICUs within the specified date range due to infections caused by gram-negative bacteria (particularly Pseudomonas spp. and Acinetobacter spp.) Six of these patients were excluded from our study because they had chronic renal failure (CRF). The remaining 20 patients (59%) had developed AKI during colistin treatment (AKI group), while 14 patients (41%) did not develop (non-AKI group) (Figure 1).

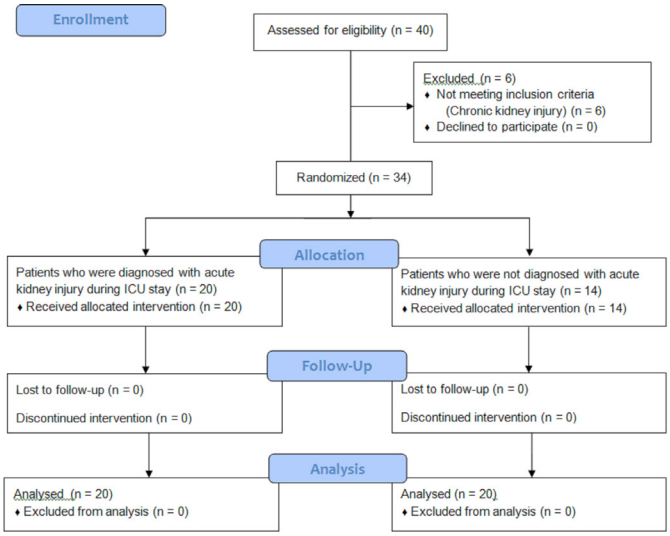

Figure 1. Working flow diagram

There was no statistical difference in AKI and non-AKI groups in terms of age, gender and length of stay in ICU (Table 2). However, the patients in the AKI group were older and stayed in the ICU for a longer period of time.

Seven of the 20 patients in the AKI group were stage III AKI according to the KDIGO criteria, while other 13 patients were stage I and II. In addition, three patients had hypoalbuminemia (<3.5 g/dL) when they admitted to the intensive care, and mechanical ventilation was required for all patients in this group.

In five of 20 patients in the AKI group, both i.v. (2x150mg) and inhaler colistin (2x75mg) use were observed. In the non-AKI group, three patients used both i.v. and inhaler colistin.

Although the comparison of the groups in terms of comorbid diseases revealed no statistically significant difference between the groups, patients in the AKI group had more comorbidities (Table 1).

Although there were nephrotoxic drugs among the drugs used by the patients in both groups, no statistically significant difference was observed between the groups (p>0.05).

There was no significant difference between the duration of colistin use, dose, albumin and hematocrit levels measured before, during and after colistin treatment, and blood and blood product transfusions (p >0.05). The duration of colistin use and doses are presented in Table 2.

Although serum creatinine values were not statistically significant before and during colistin treatment in both groups, they were found to be higher in AKI group after treatment (2.45 ± 1.06 mg/dL vs 0.87±0.56 mg/dL, p<0.05).

The duration of inotropic agent use in the AKI group (7.5 (4.8-17.2 [<2-41] days) was found to be longer than the non-AKI group (4 (2-6 [0-48]) days) (p<0.05).

Colistin-related mortality rates were found to be 50% (n = 10/20) in AKI group and 43% (n = 6/14) in non-AKI group.

Table 1. Demographic data

	AKI (n=20)	Non-AKI (n = 14)	p value
Age (year)	73 (55-78 [31-88]	66 (53-77.2 [35-85])	0.736
Female sex (n) (%)	11 (55%)	7 (50%)	1
Length of hospital stay (days)	50 (29-56 [14-96])	36 (20.5-60.5 [10-110])	0.418
Diabetes mellitus, n (%)	7 (35%)	6 (43%)	0.830
Coronary artery disease, n(%)	3 (15%)	2 (14%)	1
Chronic obstructive pulmonary disease, n(%)	1 (5%)	4 (29%)	0.139
Subarachnoid hemorrhage, n (%)	2 (10%)	1 (7%)	1
Cerebrovascular event, n (%)	2 (10%)	3 (21%)	0.622
Hypertension, n (%)	6 (30%)	6 (43%)	0.6109
Atrial fibrillation, n (%)	1 (5%)	1 (7%)	1
Congestive Heart Failure	2 (10%)	2 (14%)	1
Mitral valve failure, n (%)	2 (10%)	-	0.65
Cancer, n (%)	5 (25%)	2 (14%)	0.796
Cirrhosis	1 (5%)	-	1
Pulmonary embolism, n (%)	-	2 (14%)	0.298
Rheumatism, n (%)	2 (10%)	-	0.656
Obesity, n (%)	1 (5%)	-	1
Epilepsy, n (%)	2 (10%)	-	0.656

Table 2. Duration of colistin use and dose

	AKI (n=20)	Non-AKI (n = 14)	p value
Colistin time (days)	16.12 ± 5.86	15.75 ± 7.63	0.889
Colistin iv (mg)	190.48 ± 136.58	164.29 ± 118.37	0.551

DISCUSSION

Colistin was used for gram negative (A. baumanii, P. aeruginosa, K. pneumonia) bacteria with multiple antibiotic resistance until the 1980s, however, its parenteral use was limited due to the nephrotoxicity development. The nephrotoxicity rate of the colistin varies between 5% and 55%, while the colistin-induced AKI rates are reported to increase up to 60% (8,9,10).

Although the exact cause of nephrotoxicity has not be known yet, it may be due to many factors such as age, comorbidities, nephrotoxic drug use, obesity, colistin dose and usage duration (11,12).

In our study, the mean age of the patients in the AKI group was higher than the non-AKI group and the comorbid diseases were more than the non-AKI group. Therefore, colistin-induced nephrotoxicity rate was found to be 59%. İnci et al. (13) reported the rate of nephrotoxicity as 54.2% in patients receiving colistin treatment in the ICU.

Furthermore, since advanced general intensive care is provided in the ICU where the present study was carried out, spectrum of hospitalization of the patients was very wide-ranging. Age and duration of stay in the ICU, which have been reported to effect the development of nephrotoxicity, were found to be significantly in favor of the AKI group in our study.

In a study by Arslan et al. (14), the use of inotropic agent was found to be significantly higher in AKI group compared to non-AKI group.

Similar to this study, the duration of the use of inotropic agents were found to be longer in the AKI group in our study. Inotropic agent was used in all patients in AKI group, while three patients in non-AKI group did not receive any inotropic agent.

In addition, fluid balance of patients is important in AKI development. Fluid therapy, hourly urine monitoring and central venous pressure trends of the patients should be closely monitored particularly in the use of medicines with the risk of nephrotoxicity. In the present study, daily renal functions and fluid balances of the patients were closely monitored through invasive and noninvasive methods. Matthaiou et al. (15) reported in their study that nephrotoxicity is seen less than in the previous periods thanks to the better monitoring of patients, limitation of nephrotoxic drugs used with colistin, and increased awareness.

The duration of colistin use for more than 14 days is reported to be an important factor in the development of colistin-induced nephrotoxicity and to increase the nephrotoxicity risk four times (14). No significant difference was observed between the groups included in this study in terms of the duration of colistin use. However,

duration of colistin use was found to be longer in non-AKI group. Decrease in AKI development despite the prolonged use of colistin may be attributed to the assertion made by Matthaiou et al. (15) regarding that better monitoring, limitation of nephrotoxic drugs and increased awareness have reduced nephrotoxicity.

In their study, Yu-Ji Lee et al. (16) investigated the relationship between colistin dose and nephrotoxicity and reported that nephrotoxic patients were found to be older and their serum albumin and hematocrit levels were lower. Our findings revealed deep hypoalbuminemia (<3 g/dL) in eight patients in the AKI group, however, there was no significant difference between the groups in terms of albumin levels.

Although we are a reference hospital in the region and patients planned to start colistin in the district hospitals are referred to our hospital, the study population remained insufficient and a control group could not be established in this single-center study. For the same reason, patients are particularly heterogeneous in terms of comorbidities. These limitations have been reported in similar studies in the literature.

CONCLUSION

In conclusion, the results of this study have showed that colistin use is associated with advanced age and comorbidities, resulting in prolonged hospital stay. However, no statistically significant differences were observed because of the insufficient study population and the lack of homogeneity. Therefore, we believe that randomized controlled trials with sufficient number of patients, in which homogeneity can be achieved between the groups in terms of age and comorbidity, are needed for early detection and prevention of colistin-induced nephrotoxicity.

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