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Original Article

Comparison of clinical characteristics of patients with acute kidney injury after intravenous versus inhaled colistin therapy

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A B S T R A C T

Background: The aim of this study was to investigate the incidence and clinical characteristics of intravenous (IV) or inhaled (IH) colistin-associated acute kidney injury (AKI) using the Risk, Injury, Failure, Loss, End-stage Renal Disease criteria.
Methods: From 2010 to 2014, 160 patients were treated with IV or IH colistin. Of these, we included 126 patients who received colistin for > 72 hours for the treatment of pneumonia and compared the incidence and clinical characteristics of patients in the IV ($n = 107$) and IH ($n = 19$) groups.
Results: The patients included 104 men and 22 women, with a mean age of 69 years (range, 24–91 years). The mortality rate was 45%, and AKI occurred in 75 (60%) patients. At the end of therapy, the bacteriologic cure rate was 66%. There were no differences in the clinical characteristics between the IV and IH groups except for age. In comparison with patients in the IV group, the patients in the IH group were older (74 ± 8 vs. 68 ± 12 years, $P = 0.026$). The incidence of AKI was not different between the 2 groups (62 vs. 47%, $P =$ not significant), and there was no difference in the severity of AKI according to the Risk, Injury, Failure, Loss, End-stage Renal Disease criteria. Of the 83 patients with AKI, 6 and 1 patients underwent renal replacement therapy, respectively.
Conclusion: The incidence of AKI in patients with colistin therapy is 60% in our center. It seems that IH colistin therapy could not be better in safety than IV colistin therapy.

Introduction

Colistin is an antibiotic that was used until the early 1980s to treat infections caused by gram-negative rods [1,2]. When gentamicin and second- and third-generation cephalosporins became available, however, colistin fell out of favor because of the reported high incidence of nephrotoxicity [1–3]. However, the emergence of multidrug-resistant gram-negative bacteria such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* resulted in reconsideration of the use of intravenous (IV) colistin as a last resort for treatment of these infections [1,3,4].

Inhaled (IH) colistin has been successfully used to prevent and cure pulmonary infections in cystic fibrosis patients who are colonized with *P. aeruginosa* [5]. Recently, some authors

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reported that colistin inhalation therapy is both tolerable and safe and could be beneficial as an adjunctive therapy for the management of pneumonia due to colistin-only–susceptible *A. baumannii* or *P. aeruginosa* [6,7]. However, there have been no reports that have compared the clinical characteristics of patients with acute kidney injury (AKI) who were treated with IV versus IH therapy.

Therefore, we investigated the incidence and clinical characteristics of AKI after IH colistin compared with IV colistin using the Risk, Injury, Failure, Loss, End-stage Renal Disease (RIFLE) criteria.

Methods

Patient selection

From 2010 to 2014, 160 patients received IV or IH colistin. We included patients who had received IV or IH colistin for treatment of pneumonia. Patients were excluded if they received colistin for < 72 hours. We also excluded patients with a glomerular filtration rate of < 15 mL/min/1.73 m^2 before the initiation of colistin treatment and patients who developed AKI within 2 days of starting colistin treatment. A total of 126 patients were enrolled in this study in which the incidence and clinical characteristics between the patients receiving IV ($n = 107$) and IH ($n = 19$) therapy were analyzed. This study was approved by the Institutional Review Board of the Presbyterian Medical Center, Jeonju, Korea.

Clinical and laboratory information

Baseline demographic and clinical and laboratory data were reviewed at the time of hospitalization and during the follow-up period. The daily dosage of nebulized colistin was 150 mg divided into 2 doses, each of which was subsequently diluted in 4 mL of sterile normal saline. The solution was administered through a conventional nebulizer. The Acute Physiology and Chronic Health Evaluation (APACHE) II scores for all patients were determined on the first day of colistin therapy. AKI was defined based on the RIFLE criteria, and patients were categorized into the R, I, or F category. The estimated glomerular filtration rate (eGFR) was determined using the abbreviated Modification of Diet in Renal Disease equation [8]. The RIFLE class was determined based on the worst of the serum creatinine, eGFR, and urine output criteria. Renal replacement therapy was initiated using the standard indications.

Statistical analysis

All data are presented as means ± standard deviations unless otherwise specified. The baseline characteristics of patients in the non-AKI and AKI groups were compared using *t* tests, chi-square tests, or Fisher exact tests, as appropriate. The clinically relevant parameters or the variables that were significantly associated with the presence of AKI in the univariate analysis were included in the multivariate analysis. A *P* value of < 0.05 was considered to be statistically significant. All statistical analyses were carried out using SPSS software, version 21 (IBM corporation, New York, NY, USA).

Results

Baseline characteristics

The baseline characteristics of the 139 study participants are presented in Table 1. The patients included 104 (83%) men and 22 (17%) women, with a mean age of 69 years (range, 24–91 years). Seventy-nine patients had sepsis at the time that colistin treatment was started. The mean APACHE II score was 21.5 (range, 3–34). The mean plasma total bilirubin concentration was 1.05 mg/dL, and the mean C-reactive protein level was 11.41 mg/dL. The mean eGFR was 89 mL/min/1.73 m^2. Patients were infected with either *A. baumannii* (56%) or *P. aeruginosa* (44%). Of the 126 patients, 107 and 19 received colistin via IV or IH route, respectively. The mean duration of colistin therapy was 8.5 days. Of these patients, 75 (60%) experienced AKI and 57 (45%) died. Seven patients underwent renal replacement therapy.

Comparison of clinical characteristics between the IV and IH groups

When we compared clinical characteristics of the IV and IH colistin groups, the only differences were in age and renal function. In comparison with patients in the IV group, patients in the IH group were older (74 ± 8 vs. 68 ± 12 years, $P = 0.026$) and had worse renal function at the start of colistin treatment (1.5 ± 1.1 mg/dL vs. 1.0 ± 0.7 mg/dL; Table 2). The incidence of AKI was higher in the IV group than in the IH group (62% vs. 47%), although this difference was not statistically significant. Mortality rates were also not different between groups. In comparing the severity of AKI according to the RIFLE criteria, more patients in the IV group were classified into the failure category than in the IH group, although this was not statistically significant (Table 2). Of these, 6 patients in the IV group and 1 in the IH group underwent renal replacement therapy. Thirty-eight patients (58%) in the IV group and 7 patients (77%) in the IH group experienced renal recovery at the time of

Table 1. Clinical and laboratory findings of the 126 patients with colistin therapy

Characteristics	
Age (y)	69 ± 12
Male	104 (83)
Comorbidity	
Diabetes	38 (30)
Hypertension	65 (52)
Congestive heart failure	12 (10)
Sepsis	79 (63)
APACHE 2 score	21.52 ± 4.83
Serum creatinine (mg/dL)	1.06 ± 0.75
eGFR (mL/min/1.73 m^2)	89 ± 35
Total bilirubin (mg/dL)	1.05 ± 2.93
Serum albumin (mg/dL)	2.71 ± 0.51
Total leukocyte count (× 10^3/mL)	7.13 ± 3.65
C-reactive protein	11.41 ± 7.81
Duration of colistin treatment	8.53 ± 5.01
Platelet count (× 10^3/mL)	277 ± 157
Urinary abnormality	122 (97)
Nonoliguric	109 (87)
Inotropic use	49 (39)
Acute kidney injury	75 (59)
Death	57 (45)

Data are presented as *n* (%) or mean ± SD.
APACHE, Acute Physiology and Chronic Health Evaluation; eGFR, estimated glomerular filtration rate.

Table 2. Comparison of baseline characteristics between IV and IH groups

	IV ($n = 107$)	IH ($n = 19$)	P
Age (y)	68 ± 12	74 ± 8	0.031
Male	88 (82)	16 (84)	0.883
Comorbidity			
Diabetes	31 (29)	7 (36)	0.312
Hypertension	55 (51)	10 (53)	0.561
Congestive heart failure	8 (8)	4 (21)	0.112
Sepsis	66 (62)	13 (68)	0.383
Concomitant nephrotoxic drugs			0.432
0	69 (57)	14 (74)	
1	48 (40)	4 (21)	
2	3 (3)	1 (5)	
APACHE 2 score	21.8 ± 5.1	22.6 ± 3.6	0.944
Serum creatinine (mg/dL)	1.00 ± 0.65	1.53 ± 1.12	0.011
eGFR (mL/min/1.73 m^2)	91 ± 34	79 ± 38	0.012
Total bilirubin (mg/dL)	1.07 ± 3.16	1.00 ± 1.05	0.863
Serum albumin (mg/dL)	2.72 ± 0.53	2.57 ± 0.50	0.514
Total leukocyte count ($\times 10^3$/mL)	7.7 ± 10.2	7.2 ± 8.5	0.682
C-reactive protein	11.7 ± 7.7	9.94 ± 8.74	0.393
Duration of colistin treatment	8.4 ± 4.9	8.7 ± 5.5	0.752
Platelet count ($\times 10^3$/mL)	282 ± 158	245 ± 153	0.342
Inotropic use	44 (41)	5 (26)	0.745
Acute kidney injury	66 (62)	9 (47)	0.091
RIFLE criteria			
Risk	10 (15)	4 (45)	0.146
Injury	34 (52)	4 (45)	0.765
Failure	22 (33)	1 (10)	0.253
Recovery of renal function	38 (58)	7 (77)	0.675
Nonoliguric	91 (85)	18 (95)	0.852
Vancomycin	15 (23)	2 (29)	0.742
RRT	6 (9)	1 (10)	0.891
Death	52 (49)	7 (37)	0.452

Data are presented as n (%) or mean ± SD.
APACHE, Acute Physiology and Chronic Health Evaluation; eGFR, estimated glomerular filtration rate; IH, inhaler; IV, intravenous; RIFLE, Risk, Injury, Failure, Loss, End-stage Renal Disease; RRT, renal replacement therapy.

Table 3. Predictors of AKI

	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Age	1.037 (1.005–1.069)	0.021	1.012 (0.974–1.051)	0.544
APACHE 2 score	1.126 (1.036–1.223)	0.005	1.068 (0.965–1.183)	0.204
Albumin (mg/dL)	0.351 (0.165–0.745)	0.006	0.725 (0.272–1.929)	0.519
CRP (mg/dL)	1.081 (1.025–1.140)	0.004	1.061 (0.997–1.130)	0.063
Duration of colistin	1.381 (1.030–1.168)	0.003	1.245 (1.025–1.894)	0.008

AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio.

hospital discharge or on transfer to another hospital. By univariate analysis, age, APACHE II score, duration of colistin therapy, C-reactive protein, and serum albumin were significant predictors of AKI in the patients with IV or IH colistin therapy. Adjusting for these factors in a multivariate logistic regression analysis, duration of colistin therapy was the only significant predictor of AKI (Table 3).

Discussion

Colistin, an older polypeptide cationic antibiotic, was recently widely reintroduced in the clinical setting for the treatment of infection caused by multidrug–resistant gram-negative microorganisms. However, one of the well-known adverse effects of colistin is nephrotoxicity [1–3]. Using the RIFLE criteria, the incidence of AKI ranged from 36.0% to 60.4% [9–12]. The incidence of AKI was 60% at our institution, which was similar to previous reports. In this study, all patients who received IV or IH colistin were included. The incidence of AKI in the IV and IH groups was 62% and 47%, respectively. Although the incidence of AKI in patients undergoing IV colistin therapy has been reported, there were few reports regarding the incidence of AKI in patients treated with IH colistin, as evaluated by the RIFLE criteria. Choi et al [6] reported that 3 (25%) patients out of 12 who underwent IH colistin treatment experienced AKI. The incidence of AKI in patients treated with IH colistin in our study was higher (47% vs. 25%), which may have been due to worse renal function (79 vs. 90 mL/min/1.73 m^2) before starting colistin and higher APACHE II scores (22.6 vs. 19.5) than those included in the study by Choi et al.

Apart from the incidence of AKI, there is little published literature that has compared clinical characteristics between patients receiving IV and IH colistin. Choi et al reported that 3 of 12 patients who received IH colistin treatment experienced AKI, and thus IH colistin may be tolerable and relatively safe. In our study, there was no difference in the incidence of AKI between the 2 groups. In comparing the severity of AKI according to the RIFLE criteria, more patients in the IV group were classified into the failure category than in the IH group, although this was not statistically significant. After stopping colistin therapy due to the development of AKI, the recovery of renal function was superior in the IH group than in the IV group (58% vs. 77%), which was also not statistically significant. Therefore, IH colistin therapy may not be safer than IV colistin therapy and requires monitoring of renal function.

In case of IV colistin use, several parameters such as concomitant administration of other nephrotoxic agents, old age, long duration of IV colistin, high dose of IV colistin (> 5 mg/kg/d), and concomitant vancomycin therapy have been proposed as risk factors for colistin nephrotoxicity [13]. In the present study, duration of colistin therapy was the only significant predictor of AKI. Thus, it is important to observe renal function closely in patients with a prolonged use of IH colistin.

In this study, the patients in the IH group were older (74 ± 8 vs. 68 ± 12 years, $P = 0.026$) and had worse renal function at the start of colistin treatment (1.0 ± 0.7 mg/dL vs. 1.03 ± 0.70 mg/dL) than those in the IV group. Old age and previous renal dysfunction were noted to be risk factors for AKI [14–16]. It is likely that patients with older age and worse renal function received colistin via IH for fear of development of AKI. Balkan et al [17] also reported that colistin nephrotoxicity increased with age. Therefore, to evaluate the safety of IV versus IH colistin therapy, large prospective randomized controlled trials are needed.

This study had several limitations. First, this study has the retrospective design, including the use of data from past medical records. Second, the number of patients in the IH colistin group was too small. Therefore, a large prospective randomized controlled study is needed to compare the clinical characteristics of patients with AKI between IV and IH group. There is the possibility that isolated *A. baumanni* was not the etiology of pneumonia but colonization.

In our study, the incidence of AKI in patients undergoing colistin therapy was 60%, and there was no difference in safety

between the IV and IH colistin groups. Therefore, it is also important to monitor renal function during colistin therapy regardless of the route of administration.

Conflicts of interest

All authors have no conflicts of interest to declare.

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