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Brief Original Article

Colistin-induced nephrotoxicity and the role of N-acetylcysteine: a retrospective cohort study

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Abstract

Introduction: Colistin is associated with dose-dependent nephrotoxicity. N-acetylcycteine (NAC) may reduce the risk of concomitant acute kidney injury (AKI) due to its antioxidant properties. We report a retrospective cohort study evaluating the role of N-acetylcysteine (NAC) in the development of colistin (COL) associated nephrotoxicity.

Methodology: A single centre retrospective cohort study was conducted in a university hospital between January 2014 and June 2015. Nephrotoxicity was defined and staged per the RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) criteria. We evaluated the association between NAC use and COL-related nephrotoxicity by comparing the incidence of nephrotoxicity in patients receiving colistin with or without adjunctive NAC.

Results: Forty-six patients received intravenous (IV) COL and 46 patients received IV NAC+COL. The cumulative COL doses did not differ between the two groups ($p = 0.802$). The initial creatinine value doubled in 29 (63%) patients undergoing NAC+COL therapy and in 27 (58.7%) patients in the COL group ($p = 0.669$). The median doubling time of baseline creatinine was 6 and 7 days in the NAC+COL and COL groups, respectively. The mean hospital stay, potentially nephrotoxic agent use, and mortality rates were statistically higher for the patients receiving NAC+COL ($p < 0.005$).

Conclusions: The present study was not able to reveal any beneficial effect of NAC for patients undergoing COL therapy. The NAC+COL group had a higher baseline risk for development of AKI. However, the incidence of AKI was comparable between the groups. The results of the study would not solely exhibit the protective effect of adjunctive NAC therapy.

Key words: colistin; N-acetylcycteine; nephrotoxicity.

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Introduction

The increased prevalence of multi-resistant Gram-negative microorganisms, and particularly carbapenem resistant strains, is a potential threat to public health [1]. Colistin (COL) is still the most commonly used antibiotic regimen against carbapenem-resistant Gram-negative bacteria. However, COL often requires dose modifications based on decreased glomerular filtration rate (GFR) under therapy [2,3]. Acute kidney injury (AKI) is a frequent adverse effect of COL, with an incidence of 8-58%, particularly at high doses [4,5]. Nephrotoxicity is usually reversible but can sometimes result in chronic kidney disease (CKD) [6]. Oxidative stress plays an important role in the pathogenesis of COL-induced nephrotoxicity so the protective effects of antioxidative agents, such as ascorbic acid, lycopene, and N-acetylcysteine [NAC] have been investigated recently [2,7,8]. NAC is commonly used as a mucolytic agent, but it has powerful anti-inflammatory and antioxidant activities [9]. The protective effect of NAC against oxidative stress has been demonstrated in different types of conditions, such as sepsis, chronic obstructive pulmonary disease (COPD), and contrast-induced nephropathy [10-12]. Beneficial effects of NAC, in terms of the resolution of renal injury, have also been demonstrated [8]. Our aim was to perform a retrospective cohort analysis to evaluate the role of adjunctive therapy with NAC in reducing the risk of COL-induced nephrotoxicity.

Methodology

Patients and study design

This retrospective cohort study was performed at Ondokuz Mayis University, a 1150-bed tertiary care teaching hospital in Samsun, Turkey. Patients were enrolled retrospectively from January 2014 to June

2015 using the hospital health database. Patients receiving (IV) COL ± NAC ≥ 7 days were included the study. Exclusion criteria were patients younger than 18 years old, patients receiving NAC less than 24 hours before the first COL dose, and patients receiving renal replacement therapy or showing abnormal renal function tests (RFT) at the beginning of therapy.

Study variables and definitions

Nephrotoxicity was defined and staged per the RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) criteria (Table 1). RIFLE criteria were assessed at the time of peak creatinine

Table 1. RIFLE (Venkataraman 2007) Criteria*.

Category	Creatinine and GFR Criteria
Risk	Increased creatinine × 1.5 or GFR decrease > 25%
Injury	Increased creatinine × 2 or GFR decrease > 50%
Failure	Increased creatinine × 3 or GFR decrease > 75%
Loss	Persistent acute renal failure (complete loss of kidney function > 4 weeks)
ESKD	ESKD >3 months

*ESKD: End Stage Kidney Disease, GFR: Glomerlar filtration rate; *Modified from reference Venkataraman 2007* [18].

Table 2. Characteristics of patients.

Characteristic	Patients receiving N-acetylcystein + Colistin (n = 46)	Patients receiving Colistin (n = 46)	p-value
Age (years) median (min-max)	64.5 (22-88)	64.5 (20-88)	0.975
Male (%)	67.4	67.4	1.000
Underlying diseases			
Diabetes mellitus	4	4	1.000
Hypertension	9	8	1.000
Malignancy	10	11	1.000
Mean total hospital stay (days) median (min-max)	57 (17-227)	38.5 (12-127)	**0.006**
ICU stay (%)	28	27	0.832
Initial serum creatinine (mg/dl) median (min-max)	0.63 (0.19-1,39)	0.53 (0.18-1.39)	0.558
Highest serum creatinine (mg/dl) median (min-max)	2.0 (0.30-6.66)	1.65 (0.21-6.85)	0.361
End treatment serum creatinine (mg/dl) median (min-max)	1.73 (0.27-5.29)	1.47 (0.21-6.0)	0.785
Initial GFR median (min-max)	96.4 (48-120)	100.5 (35-120)	0.371
End-treatment GFR	41.3 (14.9-120)	37 (10-120)	0.897
Pre-treatment albumin (mg/dl) median (min-max)	2.6(1.53-4.0)	2.5(1.2-4)	0.229
Pre-treatment hematocrit (mg/dl)	30.4 (19.3-49)	31 (21-40)	0.901
COL loading dose (%)	42.2	57.8	0.144
Duration of COL use (days)median (min-max)	13.5 (6-49)	11.5 (7-40)	0.447
Cumulative COL dose (mg)	4275 (1350-17850)	3975 (1650-14250)	0.802
COL dose decrease (%)	65.1	34.9	**0.012**
Concomitant medications			
Diuretic	36	17	**< 0.001**
Vasopressor	33	15	**< 0.001**
Vancomycin	3	3	1.000
Methotrexate	0	1	0.315
Amphotericin b	1	2	0.513
NSAID	9	3	0.122
ACE inhibitors	3	3	1.000
Aminoglycoside	2	0	0.495
IV contrast	3	2	1.000
Co-administered antimicrobials			
Carbapenems	37	35	0.800
Tigecycline	13	6	0.122
Teicoplanin	16	8	0.097
Cefepime	3	0	0,242
Piperacillin tazobactam	4	2	0,677
Linezolide	2	1	1,000
Quinolones	2	0	0,495
Mortality (%)	37 (80.4)	23 (50)	**0,004**

level or worst GFR. GFR was calculated using the Cockcroft-Gault formula. Variables, including demographics; comorbid conditions; concomitant use of drugs known as nephrotoxic (including diuretics, vasopressors, vancomycin, methotrexate, amphotericin B, nonsteroidal anti-inflammatory drugs [NSAIDs], ACE inhibitors, aminoglycosides, IV contrast); co-administered antibiotics; and laboratory parameters of the patients were all enrolled from the patient charts and the hospital electronic database. The daily COL doses for the patients were 2-3×150 mg IV [5]. Our institution uses NAC as a mucolytic agent, and 2-3×300 mg once daily IV NAC (3 mL) was administered to each patient in the COL+NAC group, at least for the duration of COL use.

Statistical Analysis

Statistical analyses were performed using IBM SPSS v21. Results were presented as median (minimum-maximum) and frequency (percentage). The normality distribution of the data was tested using the Shapiro-Wilks test. Continuous data according to NAC use were analyzed with the Mann-Whitney U test. The association between statistical variations was investigated by Spearman correlation analysis. The categorical variables were compared by the Chi-square test. A value of $p < 0.05$ was considered as statistically significant.

Results

A total of 598 patients from intensive care units (ICU) and adult health care services received COL±NAC. Of these, 406 were excluded based on the baseline abnormal renal function tests (RFT), receiving COL for fewer than seven days, or having initiated NAC at least 24 hours before starting COL therapy. The remaining 92 patients met the inclusion criteria and their characteristics are summarized in Table 2. The mean age was 64.5 years. Most patients were male (67.5%). In total 46 patients (50%) were hospitalized in medical units, 31 (33.7%) in ICUs, and 15 (16.3%) in surgical units. Patients were divided into two groups: a COL and a NAC+COL group. NAC was administered IV to 46 patients as a concomitant drug. The groups were similar in terms of age, gender, and underlying diseases. The RFTs at baseline in both patient groups were normal.

The initial creatinine levels were similar in the NAC+COL group and COL group (0.63mg/dL and 0.53 mg/dL) ($p = 0.558$). In total, 29 (63%) patients in the NAC+COL group and 27 (58.7%) patients in the COL group showed doubling of the initial baseline creatinine levels ($p = 0.669$). The median doubling time of baseline creatinine was 6 (2-15) and 7 (2-14) days for the NAC+COL and COL groups, respectively. ($p = 0.638$). According to RIFLE criteria, 37 (80.4%) patients in the NAC+COL group and 33 (71.7%) patients in the COL group with normal baseline kidney function developed AKI (Table 3). No patients underwent renal replacement therapy. The renal impairment was reversible in 13 patients: 9 patients in the NAC+COL group and 4 in the COL group. The cumulative COL dose did not differ between patient groups ($p = 0.802$). Diuretic and vasopressor drugs were the most commonly used concomitant agents, particularly in patients co-administered NAC ($p < 0.005$).

The mean hospital stays were significantly longer for the patients in the NAC adjunct group ($p = 0.006$). Most of the patients in the NAC+COL group (80.4%) died and 18 of these patients died within 48 hours after discontinuation of COL. In total, 23 (50%) of the patients in the COL group died, and 17 of these patients died within 48 hours after discontinuation of COL.

Discussion

To the best of our knowledge no retrospective cohort study has investigated the association between NAC use and COL-related nephrotoxicity. This is the first study to investigate the effects of NAC in patients receiving COL. NAC administration did not prevent COL-induced nephrotoxicity. There were no changes in end-treatment GFR and creatinine levels. The most remarkable finding of the study is the similar incidence of AKI in both patient groups receiving COL with or without NAC, even though the patients receiving NAC

Table 3. Distribution of patients with nephrotoxicity according to RIFLE criteria.

Criteria	Number of patients receiving Colistin + N-acetylcystein (%)	Number of patients receiving Colistin (%)	p-value
AKI absent (%)	9 (19.6)	13 (28.3)	0.293
R	7 (15.2)	6 (13)	
I	6 (13)	12 (26)	
F	9 (19.6)	5 (10.9)	
L	15 (32.6)	10 (21.7)	
E	0 (0)	0 (0)	

were at higher risk for adverse outcomes (including AKI) owing to the concomitant potentially nephrotoxic medications, co-administered antimicrobials, and longer hospital stays. The high mortality rate in the NAC+COL group was also an important disadvantage.

Hospitalized patients experience several factors that may potentially affect the kidney, such as hemodynamic changes, hypoxia due to underlying conditions, or direct toxic effects of co-administered agents. All are closely related to the worsening of renal functions. The available literature shows that the COL dose, duration of therapy, co-administration of nephrotoxic agents, age, sex, underlying diseases, hypoalbuminemia, and severity of the disease are closely related to COL-associated risk factors [6]. NAC is a common option for maintaining airway clearance [13], so these data are particularly important for ICUs that use nephrotoxic agents intensively. NAC is known to protect against contrast-induced nephrotoxicity and may help ameliorate drug-related nephrotoxicity [14]. Similar rates of renal injury were found in patients receiving COL with or without NAC despite the disadvantages apparent in the NAC+COL arm. Therefore, in the presence of additional risk factors, NAC may decrease the risk of renal impairment in patients undergoing COL therapy.

The relationship between COL toxicity and cumulative dose has been demonstrated in previous reports [15,16]. The cumulative COL dose, as well as the duration of COL use, were all higher in the NAC+COL group, although the differences did not reach statistical significance ($p = 0.802$, $p = 0.447$). Potentially nephrotoxic drugs, particularly diuretic and vasopressor agents, were commonly used in the NAC+COL group ($p = 0.012$). The concurrent use of nephrotoxic drugs might have a role in reducing the COL dose.

Previous studies suggested that NAC has no benefit in patients with normal serum creatinine levels [17]. The beneficial effect of NAC is mostly observed in patients with pre-existing renal dysfunction, particularly in cases of contrast-induced nephropathy [10,12]. In the current study, where patients had no baseline renal impairment, a resolution of AKI in patients receiving adjuvant NAC during COL therapy was not demonstrated clearly. The median initial creatinine levels were similar in the NAC+COL and the COL groups, respectively 0.63mg/dL and 0.53mg/dL ($p = 0.558$). The median time to doubling of serum creatinine was lower, at 6 and 7 days, respectively ($p = 0.638$). AKI was reversible in 14% of the patients. The high mortality rates of the patients, particularly within the 48 hours after the discontinuation of the COL therapy (25%), precluded a resolution in patients with renal dysfunction. However, AKI acquired under COL therapy can resolve completely in subsequent months [15].

This study has some limitations. First, it is a retrospective study. NAC has not been initiated as a treatment for COL-related nephrotoxicity. The nature of the study design and patient characteristics mean that confounding clinical variables preclude a direct comparison between the two groups. In addition, APACHE scores were not available. These results underscore the need of further studies of larger groups of patients to obtain more convincing results.

Conclusion

The main concern with the use of colistin is nephrotoxicity. We therefore considered to investigate how to prevent COL-related nephrotoxicity or minimize the risk of AKI. NAC have also demonstrated utility in preventing renal injury. The NAC+COL group had prominent disadvantages such as concomitant nephrotoxic agents, longer hospital stays, and high mortality rate. We observed similar AKI incidence between the groups. This retrospectively designed study was not able to reveal any beneficial effect of NAC for patients undergoing COL therapy. The potential benefits of NAC must be investigated with well-designed prospective and long-term follow-up studies. The potential effect of NAC can also be considered to investigate among patients with end-stage renal disease and normal renal functions.

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