Evaluation of Renal Toxicity of Colistin Therapy With Neutrophil Gelatinase-associated Lipocalin

A Biomarker of Renal Tubular Damage

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Introduction. Nephrotoxicity has been a concern with new dosing regimens of colistin. This study was designed to compare nephrotoxicity of high dose and conventional dose of colistin and the ability of detecting it using neutrophil gelatinase-associated lipocalin (NGAL).

Materials and Methods. A randomized clinical trial was carried out on 40 patients with multidrug-resistant gram-negative infections assigned into 2 groups to receive high and conventional doses of colistin. Blood samples were taken 4 times for measuring serum NGAL. The incidence of acute kidney injury was also evaluated based on the risk, injury, failure, loss, end-stage renal disease (RIFLE) criteria.

Results. Baseline levels of NGAL were not significantly different between the patients on the high dose and conventional dose of colistin. The mean NGAL levels on day 10 were 762.14 ± 415.44 pg/mL and 623.67 ± 272.61 pg/mL, respectively. However, between-group analysis did not show a significant difference in the NGAL levels. The prevalence of acute kidney injury was 60% and 15% based on the RIFLE criteria, in the high-dose and conventional-dose groups, respectively (P = .003).

Conclusions. Although colistin-induced nephrotoxicity was not confirmed with NGAL levels, our findings, however, showed a higher incidence of acute kidney injury associated with high-dose colistin, defined by the RIFLE criteria. Higher levels of NGAL in the acute kidney injury patients were associated with high-dose regimen of colistin.

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INTRODUCTION

Colistin, a glycopeptide antibiotic which was available for clinical use in 1960s and was withdrawa from the market because of its toxicity, was reentered for the treatment of multidrug resistant (MDR) gram-negative infections, especially *Pseudomonas aeruginosa*, *Acintobacter baumannii*, and *Klebsiella pneumonia*.[1-4] Complementary pharmacokinetic studies about colistin and their findings and kinetic models suggested new dosing regimen for the medication did not to lead to treatment failure nor drug resistance to the last-line antibiotic therapy. Pharmacokinetic models recommendation was a loading dose of 9 or 12 million units followed by maintenance doses of 4.5 million units twice daily.[5-7]

This high-dose regimen raised concerns about drug toxicity, especially nephrotoxicity. Adverse drug reaction profile of colistin generally includes

nephrotoxicity and neurotoxicity. Nephrotoxicity is a more common and concerning adverse effect of colistin.[8-10] Reports of studies about the prevalence of nephrotoxicity of colistin varied, ranging from zero to 53.5%, associated with various regimens of the drug therapy.[11] A reason for nonuniformity of colistin was commercially available forms of parenteral dosage form of colistin. There are 2 most readily available brands of colistin for parenteral use as Coly-mycin and Colomycin, both of which contain colistimethate sodium. However, the products' labels are different and have led to mistakes. Colomycin labels show 500000 IU, 1000000 IU, and 2000000 IU of colistimethate sodium, equivalent to 40 mg, 80 mg, and 160 mg of colistimethate sodium, while Coly-mycin is labeled as 150 mg colistin base activity, equivalent to 5000000 IU or 400 mg of colistimethate sodium. Dosing recommendation for each brand was different and led to varying drug exposures.[2] Therefore, it is very important to know that which product is used in studies and whether the mentioned dose is based on colistimethate sodium or colistin base activity.

Determination of the real prevalence of renal toxicity of these high-dose colistin therapies needs more studies with defined dosing and definition of nephrotoxicity. Definition of acute kidney injury (AKI) is an important issue in such studies. Currently, serum creatinine is used for detection of AKI in clinical practice. The risk, injury, failure, loss, end-stage renal disease (RIFLE) and the Acute Kidney Injury Network classifications are usually used for evaluation of drug-induced AKI in patients. The limitation of these criteria is the basic biomarker of detection of kidney injury which is serum creatinine and is dependent on age, sex, body mass index, nutrition, and hydration status. The detection of impaired kidney function and accurate estimation of glomerular filtration rate are also not timely. Serum creatinine may reach a steady state after several days.

There are several markers introduced as novel markers for early detection of kidney injury and used in research studies. We chose neutrophil gelatinase-associated lipocalin (NGAL) as the most promising among all emerging biomarkers for AKI. Human NGAL, also known as lipocalin 2, siderocalin, or 24p3, is a 25-kDa molecule complex with neutrophil gelatinase in majority. The 25-kDa monomeric form of NGAL is secreted by injured kidney tubule epithelial cells, whereas the dimeric form is the predominant form secreted by neutrophils. Preclinical studies identified *NGAL* to be one of the most upregulated genes and proteins in the kidney very early after AKI in animal models. Expression of NGAL protein was detected predominantly in tubular epithelial cells that were undergoing proliferation and regeneration, suggesting a role in the repair process.[12-15]

Considering the current arguments and uncertainty on nephrotoxicity risk induced by different dosage regimens of colistin, the present clinical trial was designed to assess AKI associated with treatment of patients with multidrug resistant infections with different doses of colistin. We also assed NGAL as a promising biomarker for early detection of AKI in comparison with the RIFLE criteria.

MATERIALS AND METHODS

Study Design

The study was a randomized clinical trial to compare the nephrotoxicity of conventional and high-dose regimens of colistin. The study protocol was approved by the ethics committee of Shahid Beheshti University of Medical Sciences and was registered in the Iranian Registry of Clinical Trials (IRCT2014090614693N5).

The definition of a high-dose regimen was a loading dose of 9000000 IU and maintenance doses of 4500000 IU, every 12 hours,[7,16,17] and conventional dosing was 2000000 IU every 8 hours. Colomycin vials containing 1000000 IU of colistimethate sodium were used for the study.

Study Population

Eligible patients for inclusion in the study were those older than 18 years old, with a multidrug-resistant gram-negative infection (resistance to carbapenems and candidate to receive colistin therapy) admitted to a teaching hospital affiliated to the Shahid Beheshti University of Medical Sciences, Tehran, Iran. Exclusion criteria were chronic kidney disease (glomerular filtration rate < 50 mL/min), acute kidney injury before study initiation, a body mass index greater than 35 kg/m^2, and pregnancy. The study was done during May 2014 to January 2015. The sample size was measured based on an α of 0.05, a power of 80 %, a standard difference of 0.1, and a treatment difference of 0.1 mg/L. Patients were sequentially randomized, using the

Rand order of the Excel program, into 2 groups of 20 each and received high-dose and conventional doses of colistin.

Measurements

Blood samples were obtained on days 1 (as baseline before the 1st dose), 3, 5, 7, and 10 of treatment. Separated sera were stored at -70°C. Daily serum creatinine measurements were performed until day 10 and the patients were observed for occurrence of AKI based on the RIFLE criteria through the study period.[18].

Measurement of NGAL concentration was performed by the NGALBIOPORTO Diagnostics enzyme-linked immunosorbent assay kit (KIT 036, Denmark), performed in microcells coated with a monoclonal antibody to human NGAL. Bound NGAL is detected with another monoclonal NGAL antibody labeled with biotin and the assay is developed with horseradish peroxidase-conjugated streptavidin followed by the addition of a color-forming substrate.

Data Collection

Patients' characteristics and medical status including age, sex, the acute physiology and chronic health evaluation (APACHE) II score on the 1st day of colistin therapy, type of infection, causative organism of infection, and in vitro susceptibility were recorded. Co-administered antibiotics, nephrotoxic agents as well as drugs with renal adverse effects (aminoglycosides, vancomycin, nonsteroidal anti-inflammatory drugs, intravenous radio contrast agent, diuretics, and mannitol) were also documented.

Statistical Analyses

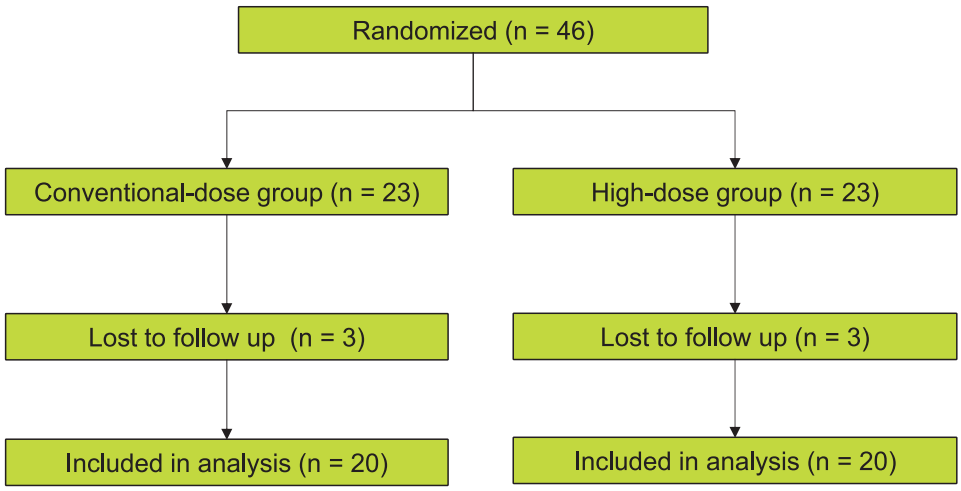
Statistical analysis was performed using the SPSS software (Statistical Package for the Social Sciences, version 21.0, IBM Corp, New York, NY, USA). Continuous normally distributed data were expressed as mean ± standard deviation and were compared using the unpaired Student *t* test. Non-normally distributed data were expressed as median and interquartile range and were compared using the Mann-Whitney U test. Categorical data were expressed as frequency and percentage of events and were compared using the Fisher exact test. For repeated measurements of serum creatinine and NGAL, a general linear model repeated measures analysis was applied. In all comparisons, a *P* value less than .05 was considered significant.

RESULTS

Participants' Characteristics

Of 46 patients who were enrolled in this study, 6 patients could not complete the study and were excluded in the 1st week of colistin therapy (3 patients in the high-dose group and 3 in the conventional-dose group) and 40 patients fulfilled the inclusion criteria and completed the study. The study flowchart is shown in the Figure.

Participants' characteristics and clinical features of their infections are summarized in Table 1. The patients were predominantly men (60% in the high-dose group and 75% in the conventional-dose



Study CONSORT flowchart.

Table 1. Patients' Characteristics and Clinical Features of Infectious Episodes*

Characteristic	High-dose Group	Conventional-dose Group	*P*
Age, y	60.95 ± 12.77	57.80 ± 21.85	.58
Male (%)	12 (60)	15 (75)	.50
APACHE II score on day 1	18.50 ± 5.88	17.35 ± 6.11	.55
Site of infection			
Lung (%)	14 (70)	14 (70)	
Blood (%)	4 (20)	6 (30)	
Central nervous system (%)	2 (10)	0	.29
Pathogen type			
Acinetobacter baumannii (%)	18 (90)	17 (85)	
Pseudomonas aeruginosa (%)	0	2 (10)	
Klebsiella pneumonia (%)	2 (10)	1 (5)	.61
Baseline serum creatinine level, mg/dL	0.90 ± 0.20	0.89 ± 0.17	.86
Baseline serum NGAL level, pg/mL	620.72 ± 296.07	586.55 ± 235.76	.70
Concomitant nephrotoxic drugs, n	0.80 ± 0.70	0.65 ± 0.49	.60
Concomitant nephroprotective drugs, n	0.85 ± 0.49	0.90 ± 0.85	.93

*Values are mean ± standard deviation or frequency (percentage). APACHE II indicates acute physiology and chronic health evaluation, and NGAL, neutrophil gelatinase-associated lipocalin.

group; $P = .50$). The mean age was 60.95 ± 12.77 years in the high-dose group and 57.80 ± 21.85 years in the conventional-dose group ($P = .58$). The major infection type was ventilator associated pneumonia or hospital-acquired pneumonia, with a frequency of 70% in each group. The mean APACHE II score was 18.5 ± 5.9 in the high-dose group and 17.4 ± 6.1 in the conventional-dose group ($P = .55$). Baseline serum creatinine and NGAL levels were not significantly different between the two groups.

Comparisons Between High-dose and Conventional-dose Groups

During the 10 days of the study period, the prevalence of AKI based on the RIFLE criteria was 60% (12 out of 20 patients) and 15% (3 out of 20 patients) in the high-dose and conventional-dose groups, respectively ($P = .01$; Table 2). Comparison of the serum creatinine differences between groups was done with repeated measures analysis, which showed serum creatinine level increased notably in both groups from the 1st day of study (before colistin therapy) to the end of the study ($P = .002$). This elevation was also significantly higher in the patients with a high dose of colistin ($P = .02$). Paired comparison of the serum creatinine levels on different sampling days of 3, 5, 7, and 10 revealed that from day 5, there were significant differences between two groups (Table 3). Baseline levels of NGAL were not significantly different between the patients of the two arms of the study. However, the repeated measures between-group analysis did not show a significant difference in the NGAL levels ($P = .26$; Table 4).

Table 2. Number of Patients Falling Under Each RIFLE Criteria Category

Acute Kidney Disease	High-dose Group	Conventional-dose Group	*P*
No	8	17	
Yes			
Risk	3	2	
Injury	7	1	
Failure	2	0	.01

Table 3. Comparison of Serum Creatinine Changes Within and Between Groups*

Serum Creatinine, mg/dL	High-dose Group	Conventional-dose Group†	*P*
Baseline	0.89 ± 0.17	0.90 ± 0.20	.86
Day 3	0.90 ± 0.23	1.00 ± 0.32	.21
Day 5	0.84 ± 0.26	1.20 ± 0.57	.01
Day 7	0.96 ± 0.27	1.40 ± 0.77	.01
Day 10	1.02 ± 0.37	1.77 ± 1.00	.01

*$P = .02$ for between-group comparisons (repeated measure test)
†$P < .001$ for within-group comparisons (repeated measure test)

Comparisons Between Patients With and Without Acute Kidney Injury

As a complementary analysis, we compared the occurrence and severity of AKI based on RIFLE criteria, irrespective of dosage regimen. In these analyses, dosing regimen itself was considered as a covariate. Overall, 15 out of 40 patients (37.5%) developed AKI. The relevant analyses are presented below. From day 3 to day 10, serum creatinine

Table 4. Comparison of Serum Neutrophil Gelatinase-Associated Lipocalin (NGAL) Changes Within and Between Groups*

Serum NGAL, pg/mL	High-dose Group	Conventional-dose Group†	*P*
Baseline	586.54 ± 235.75	620.71 ± 296.06	.70
Day 3	581.63 ± 183.57	659.42 ± 324.14	.37
Day 5	564.72 ± 209.33	683.21 ± 340.31	.21
Day 7	600.77 ± 200.59	764.59 ± 361.69	.10
Day 10	623.67 ± 272.61	762.14 ± 415.44	.33

*P = .26 for between-group comparisons (repeated measure test)
†P = .26 for within-group comparisons (repeated measure test)

Table 5. Comparison of Serum Neutrophil Gelatinase-Associated Lipocalin (NGAL) Changes Within and Between Groups of Patients With and Without Acute Kidney Disease (AKI)*

Serum NGAL, pg/mL	No AKI	AKI	*P*
Baseline	629.539 ± 275.34	569.05 ± 259.22	.50
Day 3	626.76 ± 249.18	609.83 ± 294.13	.85
Day 5	576.37 ± 292.44	704.85 ± 273.47	.18
Day 7	563.23 ± 250.18	874.25 ± 292.63	.001
Day 10	599.90 ± 338.81	883.96 ± 330.44	.06

*P = .04 for between-group comparisons (repeated measure test)
†P = .25 for within-group comparisons (repeated measure test)

levels were significantly higher in the AKI patients compared to non-AKI patients (P = .004 and P < .001 for day 3 and day 10, respectively). Comparison of NGAL between the groups with repeated measures analysis showed the difference between the two groups was significant (P < .001). The difference between groups was particularly significant from day 7 of colistin therapy (Table 5).

DISCUSSION

Currently, nosocomial multidrug-resistant gram-negative infections are one of the major concerning problems in hospitals. This has led to the re-emerging of colistin, an antibiotic which withdrew from the market because of its nephrotoxicity several years ago.[19] Pharmacokinetics studies on colistin suggested the need for higher loading and daily doses of the drug to accelerate achievement of the target levels. Dose-dependent colistin nephrotoxicity is the major concerning issue for this new dosing regimen and forced limit its usage. Worldwide trend in high-dose regimen of colistin necessitates special attention to the prevalence of nephrotoxicity of high-dose colistin therapy. In this regard, a study to evaluate prevalence of colistin nephrotoxicity and its early detection and prevention are recommended and was the effort in this study. Our study was designed to assess the incidence of nephrotoxicity with high and conventional doses of colistin regimens in a head-to-head clinical trial. We used NGAL as a biomarker for early detection of kidney injury caused by colistin. At the same time, the RIFLE classification of AKI was applied to describe the changes in serum creatinine and NGAL levels in AKI and non-AKI patients.

In a review of colistin toxicity in 2011, the prevalence of nephrotoxicity was different among trials and was reported in the range of zero to 53.5%. It was very different dosing regimens used for colistin therapy and most trials included in this review administered low doses of colistin; the maximum rate of nephrotoxicity (53.5%) was noted with an average dose of colistin administration of 4.6 mg/kg/d of Coly-mycin product (considered to be as high as 10 000 000 IU of colistimethate sodium.[20] In a retrospective study, Deryke and colleagues showed that the prevalence of nephrotoxicity of colistin therapy (5.1 ± 2.4 mg/kg/d) was 33%, which was developed during the first 5 days of treatment.[21] Pogue and coworkers have also reported a nephrotoxicity rate of 43% amongst the study patients (n = 126), 78% of whom developed AKI within 7 days of colistin therapy.[22]

In a retrospective cohort study on 132 patients, Tuon and colleagues revealed that prevalence of AKI was 25.8%. The median time to develop AKI was 7.5 days (range, 2 to 21 days).[23] Ko and colleagues divided AKI into early (within 7 days) and late (after 7 days) AKI groups. They showed patients with early AKI had a higher in-hospital mortality rate than those with late AKI. The prevalence of AKI with colistin therapy was 54.6%, of which approximately 70% developed early AKI. They concluded that early occurrence of AKI might be fatal and careful monitoring of kidney function is necessary. They also suggested further study to determine early markers of predicting AKI.[24]

In our study, the prevalence of AKI based on the RIFLE criteria was 60% (12 out of 20 patients) and 15% (3 out of 20 patients) in the high-dose group and conventional-dose group, respectively. Occurrence of AKI was significantly higher in the high-dose regimen group and the difference in serum creatinine between the two groups was significant from day 5 of colistin therapy. The mean start day of AKI was 6.5 ± 2.6 days and 7.3 ± 0.58

days for the high-dose and conventional-dose groups, respectively. Nine out of the 15 patients (60%) developed AKI within 7 days after colistin therapy and the remaining 6 patients (40%) developed AKI after 7 days. These findings are comparable to those of other studies which were mentioned above. These emphasize the importance of early detection of colistin nephrotoxicity and its prompt management.

We chose NGAL as a biomarker for early detection of AKI. The comparison of NGAL between the high dose and the conventional dose did not show any significant difference. In our study, although NGAL level increased in the high-dose arm greater than that in the conventional group, this difference was not significant. Although several studies confirmed the accuracy of urinary or plasma NGAL as a biomarker of AKI, substantial differences was observed among studies and several conditions such as acute infections, chronic obstructive pulmonary disease, pancreatitis, heart failure, systemic inflammatory syndrome, severe sepsis, and septic shock were identified which may interfere with NGAL performance as confounding factors.[25,26]

In the study by De Geus and coworkers on critically ill patients, the results showed that serum NGAL measured at intensive care unit admission was not superior to serum creatinine-derived estimated glomerular filtration rate in predicting the development of severe AKI.[25,27] Martensson and colleagues also demonstrated that plasma NGAL was a poor predictor for AKI in septic shock patients because peak plasma NGAL was not significantly different between septic shock patients with and without AKI.[28]

We usually do not know the exact onset of drug-induced AKI and thus it is difficult to define a proposed time of NGAL measurement in the patients. The superiority of plasma NGAL as an early biomarker of AKI may be restricted to the cases with known timing of kidney injury, such as major surgical procedures, cardiopulmonary bypass, or radio contrast consumption.[25,29] In these circumstances, possibility for more frequent sampling and biomarker measurement lead to more accurate results. McCullough and colleagues measured NGAL at baseline and 1, 2, 4, 6, 12, 24, and 48 hours after receiving radiocontrast in order to detect radio contrast-induced nephropathy, and they noted a significant increase in NGAL at 6 hour after drug administration.[29] The potential priority of urinary over serum NGAL has also recently been confirmed in some clinical studies showing that stress and acute leukocytes variations have a dramatic influence on serum but not on urine NGAL, thereby decreasing its specificity for detection of AKI.[12]

After dividing the patients into AKI and non-AKI groups, data analysis showed that NGAL levels were significantly different between these groups from day 7 of colistin therapy. This analysis was done for serum creatinine differences between AKI and non-AKI groups and difference between groups was significant from day 3 of colistin therapy. The difference of NGAL and serum creatinine levels between AKI and non-AKI groups was significant from day 3 and day 7 of colistin therapy for serum creatinine and NGAL, respectively; thus, in contrast to our hypothesis, NGAL does not detect AKI earlier than serum creatinine.

The result of this study showed that high-dose colistin could induce AKI earlier and more frequently than the conventional regimen. As expected, our results confirmed dose-dependent manner of kidney toxicity by colistin again. The RIFLE criteria and changes in serum creatinine may be still a good method for figuring out colistin nephrotoxicity. During colistin therapy, NGAL increased in both arms of our study and this increment was higher in patients treated with high-dose regimen but not significantly; no significance of this finding may be related to time intervals between biomarker measurements. Future studies with more frequently checking of the biomarker in a larger population (especially on critical days) will be helpful.

CONCLUSIONS

This study was designed to evaluate the prevalence of AKI and also to introduce a novel biomarker of kidney injury for detecting of colistin nephrotoxicity. According to our findings, nephrotoxicity of colistin was more likely when new recommended regimen administered for patients. This finding confirmed the dose-dependent manner of this adverse reaction. Although NGAL as a proposed biomarker in this study could not detect nephrotoxicity differences between the two study arms earlier than serum creatinine, the importance of search for proper biomarkers, considering the worldwide prescription of colistin with a new regimen, is critical.

CONFLICT OF INTEREST

None declared.

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