EVALUATION OF RENAL FUNCTIONS IN PATIENTS TREATED WITH COLISTIN

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ABSTRACT

Objective: Colistin belongs to the polymyxin group of antibiotics, of which use was ceased in previous years due to nephrotoxic side effects. However, recent trials suggest that nephrotoxicity is not observed as frequently as previously believed, and patients who develop nephrotoxicity have accompanying risk factors.

In this study, we aimed to investigate the frequency of nephrotoxicity and the risk factors that might cause nephrotoxicity in patients treated with colistin.

Material and Method: Patients who were hospitalized and treated with colistin for a minimum of one day were included in the study. The frequency of nephrotoxicity was evaluated and the risk factors that might have contributed to nephrotoxicity (older age, heart failure, hypoalbuminemia, hypovolemia, hypotension, mechanical ventilation, and other nephrotoxic drugs) were studied.

Results: The study included 67 patients. Nephrotoxicity was found in 65.7% of the patients. When the risk factors were evaluated, older age and hypotension were found to be more frequent (p=0.02 and p=0.01, respectively) in patients who developed nephrotoxicity than in those who did not. Twenty-one patients who did not develop nephrotoxicity and 42 patients who developed nephrotoxicity were found to use other nephrotoxic drugs in addition to colistin; additional drug usage increased the risk of renal failure two-fold (odds ratio: 2; CI: 0,263-15,209).

Conclusion: Nephrotoxicity is a significant and frequent adverse effect that may occur during colistin use. Patient risk factors may increase the possibility of developing renal failure. Thus, before administration of colistin, patients must be evaluated for other risk factors that may cause nephrotoxicity.

Keywords: Colistin, side effects, acute kidney injury, risk factor. **Nobel Med 2016; 12(1): 74-78**

KOLİSTİN TEDAVİSİ VERİLEN HASTALARDA BÖBREK FONKSİYONLARININ DEĞERLENDİRİLMESİ

ÖZET

Amaç: Kolistin, geçmiş yıllarda kullanıldıktan sonra nefrotoksisitesi sebebiyle terk edilen; ancak günümüzde çoklu antibiyotik direnci gösteren mikroorganizmalara karşı tek alternatif olması nedeni ile kullanımı yeniden gündeme gelen polimiksin grubu bir antibiyotiktir. Ancak son yıllarda yapılan çalışmalarda, nefrotoksisitenin geçmişte bildirildiği kadar sık olmadığı, nefrotoksisite gelişen hastalarda eşlik eden risk faktörlerinin de bulunduğu bildirilmektedir.

Bu çalışmada kolistin tedavisi verilen hastalarda nefrotoksisite sıklığının belirlenmesi ve nefrotoksisite nedeni olabilecek risk faktörlerinin belirlenmesi amaçlanmıştır.

Materyal ve Metot: Bu çalışmaya, hastanede yatan ve en az bir gün süresince kolistin tedavisi verilen hastalar dahil edilmiştir. Hasta dosya bilgilerinden, nefrotoksisiteyi etkileyebilecek diğer risk faktörleri; ileri yaş, kalp yetmezliği, hipoalbuminemi, hipovolemi, hipotansiyon, mekanik ventilasyon, nefrotoksik başka bir ilaç kullanımı olup olmadığı araştırılmıştır.

Bulgular: Bu çalışmaya 67 hasta dahil edilmiştir. Çalışmaya alınan hastaların %65,7'sinde değişik derecelerde nefrotoksisite tespit edilmiştir. Risk faktörleri incelendiğinde ileri yaş ve hipotansiyon nefrotoksisite gelişen grupta anlamlı olarak yüksek bulunmuştur (sırası ile $p=0.02$ ve $p=0.01$). Nefrotoksisite gelişmeyen grupta 21, gelişen grupta ise 42 hastanın kolistinle birlikte bir başka nefrotoksik ilaç kullandığı tespit edilmiş olup gruplar arasında başka bir nefrotoksik ilaç kullanımı açısından anlamlı fark bulunmamıştır (odds ratio: 2; CI: 0,263-15,209).

Sonuç: Nefrotoksisite kolistin kullanımı sırasında ortaya çıkabilecek önemli ve sık görülen yan etkidir. Hastaya ait risk faktörleri böbrek yetersizliği gelişme olasılığını artırabilir. Bu nedenle, kolistin verilmeden önce, hasta nefrotoksisiteye neden olabilecek diğer risk faktörleri için değerlendirilmelidir.

Anahtar kelimeler: Kolistin, yan etkiler, akut böbrek hasarı, risk faktörü. **Nobel Med 2016; 12(1): 74-78**

INTRODUCTION

Colistin belongs to the polymyxin group of antibiotics, whose use was ceased in previous years due to nephrotoxic side effects. Polymyxin antibiotics are being reconsidered because they are the sole antibiotics that can be used against multi-drug resistant microorganisms.[1] Previously, colistin was shown to be the cause of renal failure, especially in intensive care patients.[2] However, recent trials suggest that nephrotoxicity is not observed as frequently as previously believed, and patients who develop nephrotoxicity have accompanying risk factors.[3]

In this study, we aimed to assess renal functions in patients hospitalized at Afyon Kocatepe University Hospital and treated with colistin in the last three years. We also aimed to study the possible risk factors of nephrotoxicity and whether these risk factors increased the occurrence of nephrotoxicity caused by colistin.

MATERIAL AND METHOD

The study was retrospective, and the data were obtained from patient file records. Patients older than 18 years old who were hospitalized at Afyon Kocatepe University Medical Faculty Hospital between January 2010 and January 2013 and administered colistin for a minimum of one day were included in this study. The ages and genders of the patients, the wards to which they were admitted, and the locations of their infections and the microorganisms caused their infections were recorded from the patients' files.

The administered dosage of colistin, the duration of colistin usage, blood creatinine values before and after the treatment, and whether dialysis was performed were studied. Renal functions were calculated according to Risk, Injury, Failure, Loss, End-Stage Renal Disease (RIFLE) criteria, and patients were evaluated for colistin nephrotoxicity.[4] The patients without signs of nephrotoxicity were categorized as Group 1, while those with nephrotoxicity were categorized as Group 2.

From patient charts, other risk factors that may affect nephrotoxicity, including older age (>65 years old), cardiac failure, hypoalbuminemia (<3.5 gr/dl), hypovolemia (BUN/creatinine> 20/1), hypotension (<90/60 mmHg), mechanical ventilation, and other nephrotoxic drugs (diuretics, angiotensin converting enzyme inhibitors, non-steroid anti-inflammatory drugs, intravenous contrast, valproic acid, and mannitol), were identified and studied. The doses and usage durations of possible nephrotoxic antibiotics used with colistin were recorded.

In patients who developed nephrotoxicity during treatment, renal functions and infection prognosis were checked after treatment.

Table 1: Distribution of subjects according to age, gender and wards.			
	Total (n=67)	Group 1 (n=23)	Group 2 (n=44)
Gender (Female/Male)	20/47	6/17	14/30
Age (p:0.008)	61.58±18.42	53.48 ±19.61	65.82±16.46
Wards			
Surgery intensive care	6	1	5
Chest disease intensive care	9	2	7
Neurology intensive care	7	2	5
Internal medicine intensive care	4	2	2
Reanimation unit	22	8	14
Inpatient services	19	8	11

Table 2: Classification of the patients in group 2 according to Risk, Injury, Failure, Loss, End-Stage Renal Disease (RIFLE) criteria		
RIFLE Score	**Number of Patient**	**%**
Risk	5	11.36
Injury	15	34.09
Failure	23	52.27
Loss	0	0
End-stage renal disease	1	2.27
Total	44	100

Statistical Assessment

Statistical assessment of the study was performed using SPSS 15 software, Fisher's exact test, Pearson's chi-square test, and Student's t-test.

RESULTS

Eighty-four patients were found to have been treated with colistin. After the exclusion of 15 patients have chronic renal failure (CRF) before colistin treatment and two patients died during the first day of treatment with colistin, the study was conducted with 67 patients. Twenty patients were female (29.9%) and 47 were male (70.1%). Patient ages, genders, and the wards in which they were hospitalized are provided in Table 1. In 23 patients (34.3%), there was no change in renal functions during colistin treatment (Group 1), but in 44 patients (65.7%), gradual nephrotoxicity was identified (Group 2). The effects of nephrotoxicity in Group 2 patients, according to RIFLE criteria, are provided in Table 2.

Nephrotoxicity was managed with medical treatment in 32 patients from Group 2 (72.5%) while 12 patients from Group 2 (27.3%) underwent hemodialysis. The renal functions of patients who received medical treatment with colistin recovered after colistin treatment was stopped. Of the patients who underwent hemodialysis, eight died during hemodialysis treatment,

one developed chronic renal failure (CRF), and three fully recovered renal functions after colistin treatment was stopped. So after colistin treatment was ceased, renal functions returned to normal in 35 patients (79.6%), and only one patient (2.3%) demonstrated chronic renal failure (CRF).

When the infected regions requiring colistin treatment were assessed in both groups (Group 1 and Group 2), nosocomial lower respiratory tract infections were found to be the most frequent infection (56.5% in Group 1 and 61.4% in Group 2). Other reasons for colistin treatment included surgical site infection (17.5% for Group 1 and 15.8% for Group 2), nosocomial bacteremia (8.7% and 18.2%, respectively), nosocomial urinary tract infection (8.7% and 2.3%, respectively), soft tissue infection (4.3% and 0%, respectively), central nervous system infection (0% and 2.3%, respectively) and, in one patient in Group 1 (4.3%), no region of infection could be determined. The microorganisms in 43 out of 44 patients in Group 2 were Acinetobacter species, and, in one patient, both Acinetobacter and Pseudomonas were isolated. In Group 1, Acinetobacter species were detected in 21 patients and Escherichia coli were detected in one patient. One Group 1 patient was started on empiric treatment.

All patients started colistin treatment with a dose of 5 mg/kg per day. The dosage was adjusted according to changes in blood creatinine values during treatment. In twelve patients, colistin treatment was stopped due to an increase in blood creatinine levels despite dose adjustment. The average duration of colistin use in Group 1 was 10.26 ±5.18 days. In Group 2, the average duration was 7.68±4.02 days. The difference between the two groups was statistically significant (p=0.029).

Among the risk factors studied, older age and hypotension were found to be significantly higher in Group 2 compared to Group 1 (p=0.02 and p=0.01, respectively). Twenty-one patients in Group 1 and 42 patients in Group 2 were found to use other nephrotoxic drugs in addition to colistin; there was no significant difference between the two groups in terms of other nephrotoxic drug use. Comparison of risk factors between the two study groups is provided in Table 3, and comparison between the groups in terms of other nephrotoxic drug use is provided in Table 4.

All patients were checked for infection prognosis. In Group 1, 16 patients (69.7%) recovered, one patient (4.3%) did not respond to treatment, one patient (4.3%) was discharged before treatment was finished, and five patients (21.7%) died. In Group 2, 13 patients (29.5%) recovered, three patients (6.8%) did not respond to treatment, and 28 patients (63.6%) died. In Group 2,

the response to colistin treatment was five times lower compared to Group 1 (CI: 1.8-16.36), while mortality was significantly higher in Group 2 than in Group 1 (*p*=0.001). Prognosis of infection in study groups are provided in Table 5.

DISCUSSION

Colistin is effective against many gram negative aerobic bacteriae in vitro. Today, it is widely used against gram negative bacterial infections (*Pseudomonas aeruginosa*, *Acinetobacter baumannii, Klebsiella pneumoniae, Escherichia coli*), which are resistant to many drugs. In our study, colistin mostly was used to treat infections caused by highly resistant *Acinetobacter* species. In the literature, the rate of colistin-related renal failure has been reported to be between 6% and 55%.[3,5-7] The difference between the nephrotoxicity rates might arise from the varying evaluation criteria used to diagnose renal failure. In this study, we used the RIFLE classification to assess renal damage and identified an occurrence rate of 65.7%, a value higher than the rates in the literature. The difference might be due to the evaluation of renal damage by normalizing creatinine level changes against pre-treatment serum creatinine levels and by using the RIFLE criteria. Therefore, to determine nephrotoxicity, the measurement of pre-treatment serum creatinine levels and the use of up-to-date criteria are strongly recommended.

In our study, we determined that 79.6% of the patients who developed nephrotoxicity regressed after the drug treatment was ceased. In the literature, at patient follow-up 1-3 months after developing nephrotoxicity due to colistin treatment, the toxic effect had reversed in 88% of the patients. Colistin nephrotoxicity generally develops in the first week of treatment. When treatment exceeds 14 days, the risk of renal failure increases four-fold. The toxicity is also known to be dose-dependent.[3,7-13]

Colistin increases the permeability of renal epithelial cells which causes tubular defects and necrosis. This effect is known to be related to drug concentration and the duration of treatment.[13-15] But in our study, the duration of colistin usage was longer among patients who developed nephrotoxicity compared to those who did not develop nephrotoxicity. This may be due to the completion of treatment by Group 1 patients but not by the 12 patients in Group 2. In the literature, it has been emphasized that nephrotoxicity may reach high risk levels that necessitate ceasing treatment.[6, 9] In our study, colistin treatment was stopped for 12 patients because of renal damage. Eventhough the duration of the treatment was recorded, the cumulative doses of colistin administered to these patients could not be

Table 3: Comparison of the study group for factors affecting renal function

Risk Factors	Total (n=67)	Group 1 (n=23)	Group 2 (n=44)	p	Odds Ratio (confidence interval)
Nephrotoxic agent usage	63	21	42	0.60	2 (0.263-15.209)
Remain in intensive care unit	55	17	38	0.20	2.23 (0.629-7.943)
Older age (>65)	36	8	28	0.02	3.281 (1.143-9.421)
Cardiac failure	11	1	10	0.08	6.471 (0.773-54.147)
Hypoalbuminemia	56	18	38	0.49	1.759 (0.473-6.537)
Hypovolemia	17	8	9	0.20	0.482 (0.156-1.490)
Hypotension	43	10	33	0.01	3.900 (1.337-11.372)
Mechanical ventilation	57	17	40	0.08	3.529 (0.882-14.122)

Table 4: Comparison to the study groups for usage of nephrotoxic drugs other than colistin

Drugs Usage	Total (n=67)	Group 1 (n=23)	Group 2 (n=44)	p
*Beta lactam antibiotics	60	19	41	0.221
Glycopeptides	25	7	18	0.400
Aminoglycosides	8	5	3	0.112
NSAID	4	1	3	1
Intravenous contrast	4	1	3	1
ACEI	1	1	0	0.343
**Other drugs	39	13	26	0.840

*: Beta lactam/ beta lactamase inhibitors, cephalosporins, carbapenems, **NSAID:** nonsteroidal anti-inflammatory drugs, **ACEI:** angiotensin converting enzyme inhibitors, ****:** quinolones, linezolid, diuretics, valproik acid, mannitol, anti-fungal agents, anti-hypertensives.

calculated due to lack of information. Therefore, one of the limitations of this study was that we could not interpret our data in terms of a dose-nephrotoxicity relationship.

It has been reported that, in patients with renal failure, continuing colistin treatment at a reduced dose does not affect clinical response.[16] However, in our study, the clinical response was decreased five-fold in patients who developed colistin-related nephrotoxicity compared to in patients without nephrotoxicity. The use of other nephrotoxic drugs with colistin has been shown to increase the risk of renal failure.[12,13] In our study, we could not determine a significant difference between the two groups in terms of additional nephrotoxic drug use with colistin. However, when Pearson's chi-square test was used, renal failure risk in the group treated with other nephrotoxic drugs in addition to colistin was found to be two times higher. When the other risk factors were evaluated with Pearson's chi-square test, age over 65 years old was found to increase the risk of developing nephrotoxicity 3.2-fold, heart failure 6.4-fold, hypoalbuminemia 1.7-fold, hypotension 3.9-fold, and mechanical ventilation 3.5-fold. Thus, based on our results, using a combination of colistin and other

Table 5: Prognosis of infection in study groups				
	Total % (n)	Group 1 % (n)	Group 2 % (n)	p
Clinical response	43.3 (29)	69.7 (16)	29.5 (13)	0.002
Non-clinical response	5.9 (4)	4.3(1)	6.8 (3)	1
Exitus	49.3 (33)	21.7(5)	63.7 (28)	0.001
Discharged at his own request	1.5 (1)	4.3 (1)	0 (0)	-
Total	67	23	44	

drugs with a high risk of nephrotoxicity, such as other antibiotics, non-steroid anti-inflammatory drugs, or contrast substrate, increases the risk of renal toxicity.

In previous studies of intensive care patients treated with colistin, the rate of nephrotoxicity has been reported to be between 0% and 36%.[8,12,17] In our study, the rate of colistin-related nephrotoxicity was 2.2 times higher among intensive care patients. The use of mechanical ventilation has also been determined a risk factor.[18] Deryke et al. reported high nephrotoxicity risk in intensive care patients and demonstrated that nephrotoxicity risk increased with the APACHE II scores of patients with heart failure.[7] Similarly, older age, hypoalbuminemia, and use of other nephrotoxic drugs were identified as significant

risk factors in the literature.[12,17,19-21] In this study, we found that hypovolemia and older age are important risk factors for nephrotoxicity development in patients treated with colistin. Therefore, it is essential to take precautions when using colistin to treat patients with high risk factors; renal functions must be monitored closely, and nephrotoxicity must be assessed using up-to-date criteria.

In conclusion, although colistin is highly effective against multi-drug resistant gram negative microorganisms, colistin must be used with caution due to associated nephrotoxicity risk. The existence of risk factors related to renal functions in patients treated with colistin increases the possibility of renal damage. The decision to treat patients with additional risk factors of nephrotoxicity using colistin must be made carefully, and during treatment, renal functions must be monitored closely using up-to-date criteria and based on pre-treatment serum creatinine levels.

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* The authors declare that there are no conflicts of interest.

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