Colistin and Acute Renal Failure: A Centre's Experience

Kolistin ve Akut Böbrek Yetmezliği: Tek Merkez Deneyimi

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ABSTRACT

OBJECTIVE: Colistin is a polymyxin antibiotic with a polypeptide structure and is effective against gram-negative bacilli. Although its use had decreased due to its side effects, it has increased again in recent years, especially for multi-drug resistant Pseudomonas aeruginosa, Klebsiella pneumoniae, Acinetobacter and Enterobacteriaceae. In the present study, patients that received colistin at one center were retrospectively analysed in terms of nephrotoxicity.

MATERIAL and METHODS: Patients hospitalized and treated with colistin in the intensive care unit between January 2012 and August 2013 were analyzed. Demographic data; biochemical tests at baseline, daily during hospitalization and after discharge; and the initial, maintenance and total doses of colistin were evaluated.

RESULTS: The mean age was 62±13 (31-86) years for the 27 patients with 17 (63%) males that were followed-up for an average duration of 63±89 days. During follow-up, 18 patients (66.7%) developed acute renal failure (ARF) and 17 (63%) of died. There were 12 (66.7%) mortalities in the ARF group and 5 (55%) in the group without ARF (p> 0.05). The total colistin dose and leukocyte count were higher in the ARF group with 3.75±2.34 g and 12.04±5.05/mm3 than the non-ARF group at 3.32±1.86 g and 7.60±3.7/mm3 but did not reach statistical significance.

CONCLUSION: ARF increases the mortality in ICU patients. Although colistin is an effective therapeutic agent used for resistant infections, we have to avoid higher doses due to its potential side effect of ARF.

KEY WORDS: Acute renal failure, Colistin, Nephrotoxicity

ÖZ

AMAÇ: Kolistin gram negatif basillerde etkili, polipeptid yapıda bir polimiksin antibiyotiğidir. Geçmişte yan etkileri nedeniyle kullanımı azalmasına karşın son yıllarda özellikle çoklu ilaç direnci olan Pseudomonas aeruginosa, Klebsiella pneumoniae, Acinetobacter ve Enterobacteriaceae'da etkinliği olduğundan kullanımı giderek artmaktadır. Bu çalışmada, merkezimizde kolistin kullanılan hastalar nefrotoksisite yönünden retrospektif olarak değerlendirilmiştir.

GEREÇ ve YÖNTEMLER: Çalışmaya Ocak 2012– Ağustos 2013 yıllarında 2. basamak yoğun bakım ünitemizde yatarak kolistin tedavisi alan hastalar alındı. Demografik veriler; bazal, yatış sırasında günlük alınan ve taburculuk sonrası bakılan biyokimyasal tetkikler; ve kolistin başlangıç, idame ve toplamda verilen dozları değerlendirildi.

BULGULAR: Yaş ortalaması 62±13 (31-86) yıl olan 17 (%63) erkek, toplam 27 hasta ortalama 63±89 gün izlenmiştir. Tüm izlem süresince hastaların 18'inde (%66,7) akut böbrek yetmezliği (ABY) gelişmiş, 17 (%63) hasta exitus olmuştur. Mortaliteler ABY grubunda 12 (%66,7), ABY olmayan grupta 5'tir (%55) (p> 0,05). Toplam kolistin dozu ve lökosit sayısı istatistiki olarak anlamlılığa ulaşmasa da ABY grubunda 3,75±2,34 g ve 12,04±5,05/mm3 olup ABY olmayan gruptaki 3,32±.1,86 g ve 7,60±3,7/mm3 değerlerinden daha yüksektir.

SONUÇ: Yoğun bakım hastalarında ABY mortaliteyi arttırmaktadır. Kolistin, dirençli enfeksiyonlarda kullanılan etkin bir tedavi ajanı olduğu halde ABY yan etkisi göz önüne alındığında bu ilacın yüksek dozlarda kullanımından mümkün olduğunca kaçınılması doğru bir yaklaşım olacaktır.

ANAHTAR SÖZCÜKLER: Akut böbrek yetmezliği, Kolistin, Nefrotoksisite

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INTRODUCTION

Colistin is a polymyxin (Polymyxin E) antibiotic that is a mixture of the cyclic polypeptides colistin A and B. It was derived in 1949 and is effective against most Gram-negative bacilli. Potential nephrotoxicity limited the use between 1970 and 1980 with the advent of less toxic compounds (1). The bactericidal effect of colistin has still remained unchanged from the beginning (2, 3). Multidrug resistant bacteries such as *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Acinetobacter*, NDM-1 metallo-β-lactamase and Enterobacteriaceae have been shown to be susceptible (4). Colistin has recently been preferred for multidrug-resistant *Acinetobacter* infections (5,6). Intrathecal and intraventricular Colistimethate sodium has also been used for *Acinetobacter baumanii* and *Pseudomonas aeruginosa* meningitis/ventriculitis (7-10). Some studies have indicated that colistin may be useful for treating infections caused by carbapenem-resistant isolates of *Acinetobacter baumannii* (6).

The aim of the present study was to determine the risk factors and incidence for colistin-related nephrotoxicity by using the RIFLE (risk, injury, failure, loss, and end-stage kidney disease) criteria and assessing the relationship with colistin dosage.

MATERIAL and METHODS

This retrospective observational study was performed among critically ill patients in the secondary and tertiary care medical center of Merkezefendi State Hospital in Manisa, Turkey. The patients hospitalized between January 2012 and August 2013 were included and their files were analyzed. Inclusion criteria were patients aged more than 18 years who received intravenous colistin for at least 72 hours. Patients were excluded if they were receiving renal replacement therapy prior to the initiation of colistin treatment

Demographic data; biochemical tests at baseline, daily during hospitalization and after discharge; and the initial, maintenance and total colistin dose were evaluated.

Acute renal failure was defined as increase in SCr by ≥0.3 mg/dl within 48 hours; or an increase in SCr to ≥1.5 times baseline that is known or presumed to have occurred within the prior 7 days; or urine volume <0.5 ml/kg/h for 6 hours.

Results were presented as mean ± standard deviation. Pairwise comparisons were made using the paired *t* test. Fisher's exact test and the Wilcoxon rank-sum test and Chi-square tests were used to determine differences between patients with and without evidence of renal failure. $p<05$ was considered to be statistically significant.

RESULTS

A total of 27 patients met the inclusion criteria and were included in the analysis. The indication for colistin treatment was usually Acinetobacter baumannii infection. Twenty (74%) patients were diagnosed with a pulmonary infection (pneumonia and chronic obstructive lung disease), three (11%) were complicated with cerebrovascular accident, and four (14%) were diagnosed as peritonitis, candidiasis and urosepsis. One third of the patients received colistin monotherapy, while the rest were treated with combined therapy with other antibiotics, mostly imipenem/cilastatin sodium according to the culture antibiogram results.

The mean age was 62±13 (31-86) years for the 27 patients with 17 (63%) males. The mean follow-up duration was 63±89 days. During the follow-up, 18 patients (66.7%) developed acute renal failure (ARF) (Figure 1), 17 (63%) of died. There were 12 (66.7%) mortalities in the ARF group and 5 (55%) mortalities in the non-ARF group ($p> 0.05$) (Table I). There were 7 (39%) diabetic patients in the ARF and 3 (33%) in the non ARF group ($p> 0.05$). Although the difference between the groups for total colistin dose and leukocyte count did not reach statistical significance, they were higher in the ARF with 3.75±2.34 g and 12.04±5.05/mm3 than the non-ARF group at 3.32±1.86 g and 7.60±3.7/mm^3 (Figure 2).

DISCUSSION

Multidrug resistance of certain bacteria has lead us to consider older antibiotics such as polymyxins that were no longer used in routine practice due to the development of less toxic antibiotics. Colistin have recently been used for nosocomial infections, especially in intensive care units with the emergence of multiresistant bacteria including those resistant to quinolones, β-lactams and aminoglycosides (11-13). However, the adverse effects of nephrotoxicity (mainly acute renal failure) and neurotoxicity must be considered. Fever, eosinophilia, urticaria-like allergies, pain on intramuscular injection and thrombophlebitis (iv injection) are also important (14,15).

Polymyxin B is generally used at a dose of 1.5 to 2.5 mg/kg/day (1.0 mg of polymyxin B sulfate = 10,000 IU) in patients with

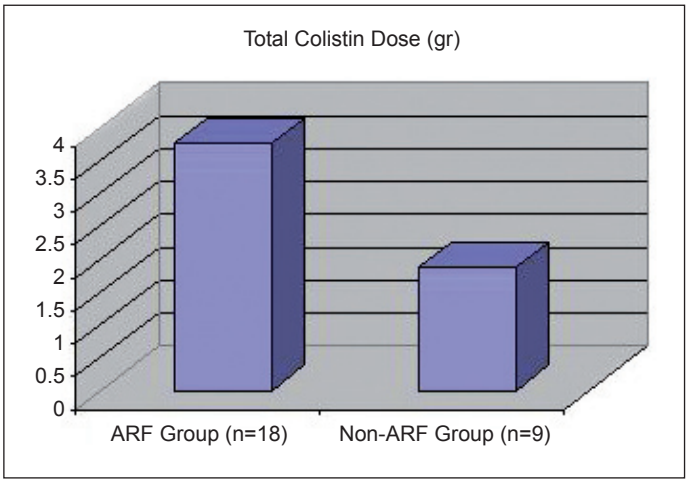

Figure 1: *Colistin dosage and acute renal failure.*

Table I: Clinical and demographic characteristics of the patients according to nephrotoxicity.

		ARF Group (n= 18)	Non-ARF Group (n= 9)	p
	Age (year)	64.8±.12.8	56.9±.14.4	N.S
	Mortality (%)	12 (66.7)	5 (55)	N.S
Colistin	First dose (g)	0.33±.0.11	0.30±.0.08	N.S
	Maintenance dose (g)	0.30±.0.13	0.28±.0.12	N.S
	Treatment time (days)	11.33±.5.68	10.78±.3.67	N.S
	Total dose (g)	3.75±.2.34	3.32±.1.86	N.S
Basal	Creatinine (mg/dl)	0.88±.0.57	0.76±.0.31	N.S
	Glucose (mg/dl)	122.2±.53.9	121.2±.28.7	N.S
	Urea (mg/dl)	58.2±.70.3	49.4±.42.4	N.S
	Creatinine (mg/dl)	0.93±.1.02	0.71±.0.65	N.S
	Sodium (meq/L)	137.9±.4.6	141±.5.3	N.S
	Potassium (meq/L)	5.44±.7.63	3.46±.0.30	N.S
	Hb (g/dl)	9.77±.1.15	9.91±.1.27	N.S
	WBC (/mm3)	11.68±.5.12	10.88±.3.40	N.S
	Plt (/mm3)	264.7±.104	318.7±.121.1	N.S
	AST (U/L)	32.7±.28	45.4±.42	N.S
	ALT (U/L)	25.9±.13.4	53.4±.42	0.02
	CRP (mg/L)	67.51±.8.55	47.98±.22.02	N.S
Final	Glucose (mg/dl)	113.8±.55.6	87.7±.18.7	N.S
	Urea (mg/dl)	98.4±.74.7	45.7±.50.3	N.S
	Creatinine (mg/dl)	2.00±.1.24	0.95±.0.84	0.03
	Sodium (meq/L)	138.2±.5.4	139.3±.4.7	N.S
	Potassium (meq/L)	3.74±.0.76	3.56±.0.69	N.S
	Hb (g/dl)	9.52±.1.28	10.06±.1.24	N.S
	WBC (/mm3)	12.04±.5.05	7.60±.3.7	0.03
	Plt (/mm3)	243.5±.130.6	343.5±.146.9	N.S
	AST (U/L)	31.0±.28.07	19.0±.6.36	N.S
	ALT (U/L)	18.9±.13	19.3±.10.7	N.S
	CRP (mg/L)	58.7±.17.8	48.1±.8.2	N.S

ARF: Acute renal failure, **N.S:** Non significance.

normal renal function (creatinine clearance >80 mL/min) (16). In abnormal renal function, it is recommended that a dose of 2.5 mg/kg be given on the first day, adjusting the subsequent doses according to creatinine clearance (CrCl). Between 30 and 80 mL/min, 1.0 to 1.5 mg/kg/d should be administered to these patients. With a CrCl < 30 mL/min, the dose ranges from 1.0 to 1.5 mg/kg every 2 or 3 days; and in anuric patients, administration of 1.0 mg/kg is recommended every 5 to 7 days (17). There are conflicting reports on colistin removal by dialysis. Some studies suggest an additional dose in patients undergoing continuous venovenous hemodiafiltration (18) while others do not (19).

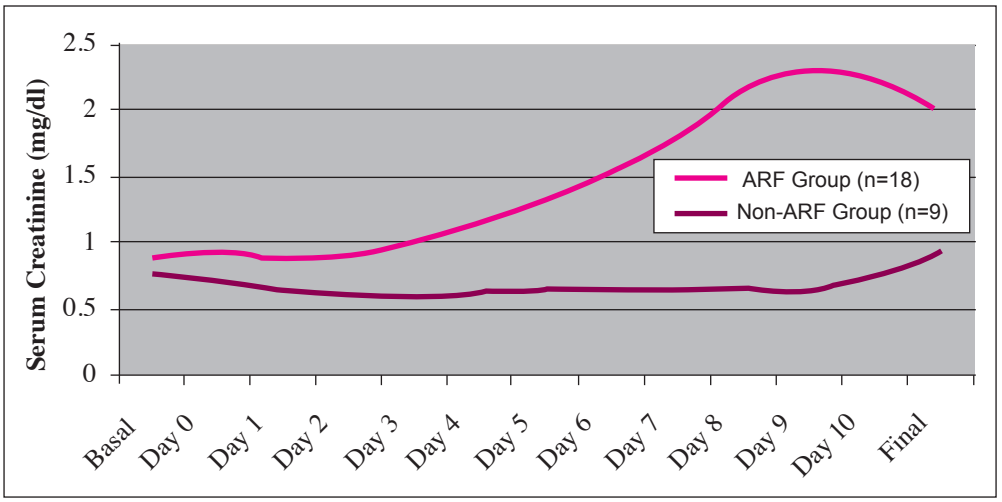

Figure 2: *Renal functions.*

Nephrotoxicity rates have ranged from 6% to 14% in some recent studies and from 32% to 55% in others (20-24). In addition to this wide range, different definitions of nephrotoxicity, differences in dosages, and a lack of control of risk factors for nephrotoxicity have complicated an understanding of this adverse effect (25). Furthermore, colistin nephrotoxicity is usually assessed in retrospective studies (26, 27), which make it difficult to reach conclusions. In the present study, a total of 27 patients were followed-up for an average of 63±89 days. During the follow-up, 18 patients (66.7%) were diagnosed with acute renal failure (ARF).

Joshua et al. retrospectively evaluated 66 patients, receiving colistin in the intensive care unit, for the nephrotoxicity adverse effect by using RIFLE criteria and found 45% of the patients had some degree of renal injury, and 21% of the patients needed to stop therapy due to nephrotoxicity (28). In the present study we used the RIFLE criteria to evaluate renal functions. Although we expected to find tubular toxicity we could not definitely diagnose it due to lack of urinalysis in all patients. The limited number of urinalysis results revealed microscopic hematuria and non-nephrotic proteinuria.

The adverse effect of renal injury, especially acute renal failure (ARF), is the major limiting factor for the use of these antibiotics. An increase in the levels of renal function tests and a decrease in CrCl, in addition to proteinuria, hematuria, cylindruria and oliguria, suggest renal dysfunction. The mechanism is probably related to the d-aminobutyric acid and fatty acid content of the molecule, and resembles the therapeutic effect of the antibiotic on the outer bacterial membrane. Membrane permeability increases, facilitating the flow of cations, anions and water and causing edema and cell lysis. We believe that the action is dependent upon the quantity and the duration of exposure to the antibiotic (29). The total colistin dose was not significantly higher in the ARF group than the non-ARF group in our study, maybe due to the small number of cases included in the study.

A study on the nephrotoxicity of colistin reported patients clinically diagnosed with drug-related acute tubular necrosis, with histological confirmation in three of them (33). Beirne et al. also reported acute interstitial nephritis due to hypersensitivity to this antibiotic (31).

Increased age, diabetes and obesity have been shown to be the risk factors of nephrotoxicity in patients receiving colistin (35) but we did not find a significant difference perhaps to the small number of cases.

Nephrotoxicity is not always seen. Dalfino et al. showed that a high-dose, extended-interval colistin regimen in severe infections due to gram-negative bacteria had high efficacy without significant renal toxicity (36).

In conclusion, reports on the renal side effects of polymyxins are found in wide range in different studies. The various definitions of ARF do not allow for more precise conclusions. It is particularly difficult to predict to what extent these drugs contribute to nephrotoxicity as most patients treated with this antibiotic have confounding factors that predispose to renal dysfunction. The nephrotoxicity of these drugs is therefore likely lower than the prevalence rates reported. It is important to take preventive measures such as maintenance of volume status of the body and being careful with the administration of other potentially nephrotoxic drugs, in addition to the careful daily renal function check, for renal protection. ARF increases the mortality in patients treated in the intensive care unit. In the present study, more than half of the patients died. Mortalities in the ARF group were slightly higher than in the non-ARF group. Although colistin is an effective therapeutic agent used for resistant infections; we recommend avoiding higher doses due to its side effect of ARF.

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