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EVALUATION OF DAILY CHANGES OF GLOMERULAR FILTRATION RATES IN PATIENTS RECEIVING COLISTIN DUE TO ACINETOBACTER INFECTION IN INTENSIVE CARE UNITE

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ABSTRACT

Aim: To examine relationship between the frequency of secondary nephrotoxicity, mortality rates and daily glomerular filtration rate [GFR] in patients receiving colistin due to acinetobacter infection in Intensive Care Unit [ICU] at the Adıyaman University Medical Faculty Hospital, Adıyaman, Turkey. **Materials and Methods:** Twenty-nine patients receiving colistin for at least 3 days due to acinetobacter infection were included in the study between the dates of January 2014 and January 2016. Age, gender, hospitalization period, the date of positive culture, hospitalization diagnosis, laboratory parameters and patients' survival condition were documented from the hospital records. GFR was calculated by Modification of Diet in Renal Disease [MDRD] formulation at the initial day and third day of colistin and creatine levels of patients were recorded for 3 days. Patients having creatinine level of more than 1.5 prior to initiation of colistin and patients receiving renal replacement therapy were excluded from the study. Double serum creatinine after therapy and/or 50% reduction of GFR values were defined as renal function disorder or nephrotoxicity. **Results**: Of the patients, 14 were male and 15 were female. The mean age of patients was 72.1±18.7. A statistically significant reduction was detected in daily GFR values [$p<0.01$]. Among the 29 patients, 24 died. The mean hospitalization period of patients was 27.7±13.5. Renal function disorder was detected in 16 [55.1%] of patients. **Conclusion:** Nephrotoxic effect of colistin was shown in various studies. However there isn't any data in the literature about the daily GFR observation in the detection of the colistin nephrotoxicity. Thus herein we examined nephrotoxicity rates by daily GFR values for the first time in the literature. The rates of nephrotoxicity were 55,1%.

KEYWORDS: Colistin, acinetobacter, nephrotoxicity, glomerular filtration rate, creatinine.

INTRODUCTION

Colistin is one of the old and specific agents with ever-increasing importance in day by day and it has been used for the treatment of resistant gram negative microorganisms. Although Colistin had been used frequently in the 1960s, its usage was reduced due to nephrotoxic adverse effects. Recently, ever-increasing number of resistant gram negative bacteria and limited number of antibiotics caused preferability of colistin again in the treatment.

Ventilator-associated pneumonia [VAP] occurs 48 hours after intubation in patients receiving mechanical ventilation [MV].[1] Endotracheal tube and as well as prolongation of intubation period are important factors.[2,3] Pneumonitis consists of 20% of hospital acquired infections and 40% of them are ICU infections. It is one of the most common nosocomial infections in ICU. While gram positive bacteria are active in developing pneumonitis during the first week of MV, acinetobacter and other multi-antibiotic resistant bacterias appear as from the fifth day of MV.[4-5]

Acinetobacter is a gram negative, oxidase negative and non-fermentative coccobacilli. Acinetobacter are the primary reasons of hospital infections recently, and they are significantly related to morbidity and mortality.[6-7] Acinetobacter are generally resistance to antibiotics, and therefore, it has a difficult treatment and causes hospital-acquired opportunist infections due to this resistance.[8-9] Since acinetobacter has high mortality rates, therapy is initiated by considering the adverse effects of colistin. The most significant side effects are nephrotoxicity and neurotoxicity. Renal toxicity mechanism is still unclear, however, development of proximal tubulopathy and reversible nephrotoxicity have been determined in certain studies.[10-11] Risk factors enhancing nephrotoxic adverse effects include advance age, previous renal deficiency, hypoalbuminemia and use of non-steroid anti-inflammatory and vancomycin during the therapy.[12,13]

In this retrospective study, renal toxicity rates and factors affecting this toxicity were examined in patients having normal renal function, receiving therapy for at least three days and in whom nephrotoxicity was calculated by accepting decreased GFR and double serum creatinine, and who received colistin as a result of acinetobacter isolated in tracheal aspirates culture.

MATERIALS AND METHODS

Twenty-nine patients in whom colistin was initiated as result of Acinetobacter spp. proliferation in their endotracheal aspirates cultures in IICU of our hospital were included in the study. Patient files were scanned retrospectively. Age, gender, hospitalization period, the date of positive culture, hospitalization diagnosis, laboratory parameters and patients' survival condition were documented. GFR was calculated by Modification of Diet in Renal Disease [MDRD= 186 x [serum creatinine] – 1.154 x [Age] – 0.203 x [0.742 Woman] x [1.210 black race] formulation at the initial day and third day of colistin admission. Patients having creatinine levels of more than 1.5 prior to initiation of colistin and patients receiving renal replacement therapy were excluded from the study. The other exclusion criterias were age under 18 and positive culture results at the first 48-hour of hospitalization. Double serum creatinine after therapy and/or 50% reduction of GFR values were defined as renal function disorder or nephrotoxicity. Initial dose of colistin was 4-6 mg/kg/day.

All the analyses were performed using the SPSS for Windows [version 21.0; SPSS/IBM, Chicago, IL]. Descriptive statistics, T test were used when suitable. The statistical significance level was accepted as a P value of less than 0.05.

RESULTS

Among the 29 patients included in the study, 24 died [87.75%]. The mean hospitalization periods of patients were 27.7±13.5. Of the patients, 2 patients died at the fourth day of therapy, 2 patients died at the fifth day of therapy, 4 patients died at the sixth day of therapy and 2 patients died at the seventh day of therapy. 14 patients were male and 15 patients were female. The mean ages of patients were 72.1±18.7. The mean number of culture positivity detection days was found as 13.1±8.9. Renal function disorder was detected in 16 [55.1%] patients after initiation of colistin. Five of the patients [17.24%] received hemodialysis therapy during hospitalization after initiation of colistin therapy. Of the patients, 22 were followed up under MV from the beginning of therapy. MV was not required in 7 patients. Of these patients, 4 were discharged from the hospital. Of the patients followed under MV, 1 patient having tracheostomy was discharged with home-type ventilator. None of the five discharged patients received inotrope support. Demographic and clinical characteristics of patients were summarized in Table 1. At the third day of therapy, a statistically significant reduction was detected in GFR values [p<0.01] [Table 2,Figure 1].

Table 1: Demographic and clinical characteristics of patients.

Parameter	n% or mean ±SD
Age	72.1±18.7
Gender[male/female]	14/15 [48.3%/51.7%]
Mean hospitalization period	27.,7±13.5
Exitus	24 [82.75%]
Mean day of culture proliferation	13.1±8.9
Renal function disorder/frequency	16 [55.1%]
Patients receiving renal replacement therapy	5 [17.24%]
Patients receiving inotrope support	16 [55.17%]
Patients receiving MV support	22 [75.86%]

Table 2: Comparison of GFR values at the initial and third day of the colistin therapy.

Parameter [mL/min]	MEAN±SD	95% CL	P values
Initial day GFR	90.2±16.8	83.8-96.6	**<0.01**
3rd day GFR	78.3±28.05	67.6-89.03	

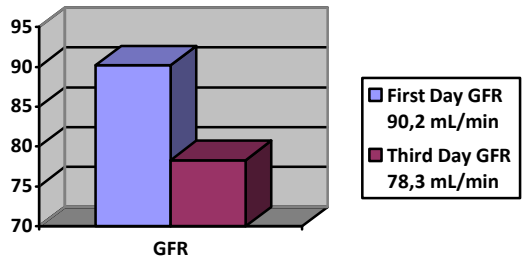

Figure 1: Grafic of the daily GFR changes.

DISCUSSION

Colistin which is a bactericidal antibiotic had been used before 1960s for the treatment of infections caused by gram negative bacteria. The use of colistin was terminated due to its adverse effects and presence of safer drug in 1980s. The inappropriate, frequent and long-term use of broad spectrum antibiotics causes the proliferation of resistant microorganisms. Recently, nosocomial infections associated with resistant gram negative microorganisms have become one of the health problems in ICUs. Therefore, colistin which was

abandoned due to its nephrotoxic and neurotoxic adverse effects has been used again recently.

Acinetobacter has a low virulence so it rarely causes infections in healthy individuals. However, it can cause system and organ diseases in patients having failures in their immune response and systems especially in ICUs, in where invasive approaches and use of broad spectrum antibiotic are very common.[9] The requirement of MV is more frequent in-patients in ICUs for a long time. It is known that the more number and frequency of invasive procedures, the higher development rate of acinetobacter infection. In a study conducted on the patients with acinetobactor infection, a correlation was determined between the extended hospitalization period in ICU and risk of acinetobacter development.[14] In the present study, the hospitalization period of patients receiving therapy due to acinetobacter complied with these results [Hospitalization period= 27.7±13.5].

Since polymicrobial agents reaching to lung parenchyma as a result of violating hygiene rules during endotracheal aspiration due to the leakage of bacteria colonized in oropharynx and upper gastrointestinal system around the endotracheal tube balloon via microaspiration acts as VAP factor, VAP is polymicrobial in the ratio of 25–46%. In addition, presence of endotracheal tube negatively influences coughing reflex and mucociliary functions, and disrupts host defense and increases liability for infections. While gram positive bacteria are active in developing pneumonitis during the first week of MV, acinetobacter and other multi-antibiotic resistant bacteria appear as from the fifth day of MV.[4-5] In the present study, the mean day of positive endotracheal culture was 13.1±8.9 and 22 [75.86%] patients received MV support, so it might be concluded that acinetobacter, multi-antibiotic resistance gram-negative bacteria, was a disease factor.

In studies investigating nephrotoxicity associated with colistine, gram negative bacterias such as acinetobacter and pseudomonas were analyzed together; however, in this present study only acinetobacter was studied. In certain studies investigating nephrotoxic effects of colistin, nephrotoxicity was found at varying rates, between 6% and 14%, or 32% and 55%.[16-18] There might be a relationship between the use and exposure time of colistin and variations in nephrotoxic adverse effect studies, in patients' renal functions, and identification criteria of renal toxicity might be dose.

The connection of nephrotoxic adverse effects with total dose or daily dose is not known exactly. On the other hand, it is thought that extended therapy period might play a role in increasing adverse effects. Renal toxicity was shown to appear within the first week in certain studies.[18-20] In most of the studies, the time of nephrotoxicity was not reported. Our studies differs from others in terms of being the first study calculating GFR at the first 7 days of therapy and detecting significant decreased GFR results in the first 3 days [$p<0.001$].

Mortality rate of acinetobacter infections are varies according to various factors, and it has been known as between 50 and 60%.[21] In the present study, mortality rate was detected as 82.75%. The reason of elevated mortality rate was considered due to the severity of primary underlying disease and high mean age. We could not compare our patients with a value identifying the severity of disease as it was a retrospective study and APACHE scores were not recorded. However, the high number of patients receiving MV [75.86%] and inotrope support [55.17%] might suggest high APACHE scores and accordingly high secondary mortality rate. The increase in the number of concomitant diseases in elderly ICU patients affects therapy choice and as well as increases the rates of mortality and morbidity.[22] In a study conducted by Boumendil et al. they found higher ICU mortality rate in advanced-elderly patients in comparison to young-elderly patients.[23] In the present study, the high mean age was considered to make a contribution to high mortality rates secondary to acinetobacter.

Mortality associated with acinetobacter was observed in patients receiving MV support.[24] Likewise, the non-requirement of four of five surviving patients to MV, and the requirement of MV support in 21 of exitus patients supported these results.

Previous studies showed that the use of antibiotics was important for resistant acinetobacter infections and inappropriate antibiotic use was one of the reasons increasing the mortality rate.[25-27] In our study, the range of using different types of antibiotics was determined as 1 to 6 until obtaining a positive acinetobacter culture result in all patients. Patients having renal function disorder were excluded from the study; however, history of using nephrotoxic antibiotic was present in 25 patients before initiating colistin therapy [carbapenem, vancomycin, tazobactam/piperacillin, candisept, etc.]. This situation was considered as the contribution of nephrotoxic antibiotic on elevated nephrotoxicity and mortality rates.

In conclusion, the previous study is important in terms of revealing that colistin-related nephrotoxicity arises sooner than usual according to the GFR calculation, and mortality rate might change in accordance with age, severity of disease and receiving MV. The limitations of the study are few patient number and undefined APACHE scores. Finally we hope that the daily GFR observation in the diagnosis of nephrotoxicity will contribute to the medicine literature. Further studies with large populations will illuminate this subject.

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