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ORIGINAL ARTICLE

Efficacy Assessment of High Dose Colistin against Carbapenem-Resistant Gram-Negative Bacteria (CR-GNB) in Critically Ill Patients: A Retrospective Non-Inferiority Trial

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ABSTRACT

Background: Colistin is an effective treatment option, recommended for carbapenem resistant gram-negative bacilli (CR-GNB) in critically ill patients. Due to high nephrotoxicity, dose management of Colistin is a tough decision to make. At standard dosage the efficacy of Colistin is not well defined. Consequently, strategies involving higher dosages were suggested.

Objective: To evaluate the high dose of Colistin as non-inferior to standard dose in the treatment of CR-GNB in critically ill patients.

Study Design: Retrospective comparative study

Place and Duration of Study: Intensive Care Unit, King Saud Medical City Riyadh, Saudi Arabia from 1st January 2015 to 31st December 2017.

Methodology: One hundred and ninety two patients that met the inclusion criteria from all participants were further divided into two groups. Group H (High dose) given the high dose of Colistin (9 million units intravenously (IV) loading dose, and then 9 million units/day in 2 or three divided doses) whereas group S was administered with standard dose (no loading dose, 6 million units/day). The primary endpoint of the study was the assessment of nephrotoxicity after the start of Colistin and secondary endpoints were the mortality within 14 days of commencing Colistin along with clinical effects and microbial clearance upon completion of treatment.

Results: The results of the study established the non-inferiority of high dose of Colistin for the renal safety and also showed significant improvement in microbial clearance and length of ICU stay as compared to the standard dose. The other secondary end points such as mortality ($p = 0.99$), length of hospital stay ($p = 0.39$), and global improvement (p value of 0.06) revealed no significant difference between the two groups.

Conclusion: The high dose of Colistin for the treatment of carbapenem resistance gram negative bacilli (CR-GNB) was as safe as the standard dose for renal safety. But we also found that it also accelerates microbial clearance and reduces the time spent in the intensive care unit.

Key words: Colistin, Colestimethate sodium, Gram negative bacteraemia, Sepsis, Multi-drug resistant organisms, Acute kidney injury

INTRODUCTION

Colistin (Polymyxin E) is a rapidly acting bactericidal antimicrobial agent that possesses effect against multi-drug resistance (MDR) Gram negative bacteria (GNB) such as Pseudomonas aeruginosa, Acinetobacter baumannii, and Klebsiella pneumonia.[1] Unfortunately, the optimal dose of Colistin for multidrug-resistant gram-negative bacteria (MDR) remains uncertain, particularly in critically ill patients previous because most of the studies were weak as a result of lack of randomization and limited sample size. It is a well-known fact that frequent use of broad-spectrum antimicrobial therapy is associated with increase in multidrug resistant gram-negative bacteria.[2]

The use of Colistin has resurged in the last decade for the treatment of MDR-GNB, because of increased incidence of MDR infections and the lack of development of effective new antimicrobials.[3,4] Colistin is administered as inactive prodrug Colestimethate Sodium (CMS) which is hydrolyzed to Colistin in human plasma. Colistin binds to lipopolysaccharides and phospholipids in the outer cell membrane of gram-negative bacteria. It competitively displaces divalent cations (Ca2+ and Mg2+) from the phosphate groups of membrane lipids, which leads to disruption of the outer cell membrane, leakage of intracellular contents and bacterial death.[5] However, when early clinical reports showed high incidence of nephrotoxicity with Colistin, its use was replaced by less toxic antibiotics, or was restricted for cystic fibrosis patients with severe pulmonary infections.[6,7]

Carbapenem have been serving as the backbone for the treatment of multidrug resistant gram-negative bacilli, but emerging resistance of GNB against the carbapenem group is alarming and compelling the scientists to find an appropriate alternative.[8] In this context the Colistin is considered an effective drug against Carbapenem resistant Gram-Negative Bacteria (CR-GNB). In the present study, we aimed to assess the efficacy of different dosage of Colistin in critically ill patients admitted in ICU of King Saud Medical City, Riyadh, Saudi Arabia.

MATERIALS AND METHODS

This is a retrospective observational cohort study carried out at the Intensive Care Unit (ICU) of King Saud Medical City (KSMC). KSMC is a tertiary care referral hospital, and the largest Ministry of Health Hospital in Riyadh, Saudi Arabia. We retrieved the data of patients treated with Colistin due to CR-GNB positive cultures during the period between 1st January 2015 and 31st December 2017. All cases were screened for the following inclusion and exclusion criteria. Total of 182 patient's age greater than 18 years both male and female were included in the study populations. Clinical evidence of sepsis (fever > 38.4ºC or < 36.5ºC – Leukocytosis >11,000 / ml) or severe sepsis/septic shock (mean arterial pressure (MAP) <65 mmHg and/or use of vasopressors), Colistin regimen was completed for at least 72 hours and positive culture of multi-drug resistant organisms(MDRO) at the start of Colistin therapy were included. Immunocompromised, end stage renal disease or patients on dialysis (Continuous Renal Replacement Therapy, Intermittent Hemodialysis, or Peritoneal Dialyses), Pregnant females were excluded.

The patients were further divided into two groups; **High dose group (H)**: patients received Colistin loading dose of 9 million units intravenous (IV), and subsequently maintained on a daily dose according to the renal assessment and **Standard dose group (S)**: Patients in this group were not loaded with Colistin, and maintained on doses according to their renal function. Clinical pharmacist of ICU kept a close eye on dosing in both groups.[9-12] (Table-1).

Demographic and baseline characteristics were collected at the start and during the course of treatment which included daily urea, creatinine clearance, intake and output, leukocytic count, temperature, and mean arterial pressure (MAP). Mortality also noted after the completion of 14 days. We also recorded the hospital outcome of the patients such as ICU and hospital length of stay (LOS), and evaluated all patients with regards to clinical improvement, bacteriological clearance (negative cultures), global improvement (both Clinical and bacteriological), and occurrence of kidney injury. Clinical improvement was considered if after 14 days of Colistin treatment or on the last day of Colistin use, the patient had no fever, leukocytic count less than 11,000, MAP > 65 and patient was not on vasopressors support. Microbiological improvement was considered if there was a negative culture for CR-GNB (from the same site as the previously positive one) within 14 days after the initiation of Colistin therapy or the nearest next culture after stopping Colistin. Only patients with both clinical and microbiological improvement were considered to have global improvement. Renal safety was evaluated based on the RIFLE criteria.[13] patients whose renal functions did not change or progressed to only risk (R) according to RIFLE criteria were considered to have had no significant kidney injury, whereas patients whose renal functions progressed to: Injury, Failure or Loss on the RIFLE criteria were considered to have had developed kidney injury. Primary outcome of the study was to evaluate high dose Colistin's non inferiority to standard dose with regards to renal safety, secondary outcomes were high dose Colistin efficacy in terms of clinical improvement, microbiological improvement, and global improvement. Other secondary outcomes included binary (dead or alive) hospital outcome, and average ICU and hospital length of stay. This study was approved by the institutional review board and ethical committee(IRBEC) with waiver of consent, since it was a retrospective study, based on data of patients previously admitted to ICU, and the management procedure was entirely up to the attending physician, without any interference from the researchers.

Studies evaluating the rate of kidney injury with standard dose Colistin report variable results, from as high as 40%[14], to rates as low as 14%[15], mostly around 30%.[16-18] Based on the published literature we assumed a proportion of patients without kidney injury in the standard dose group of 75%, and decided on a non-inferiority margin of an absolute difference of 15 percentage points. Given these assumptions, non-inferiority may be claimed if the single tailed lower boundary of the 95% CI of the proportion of patients without kidney injury in the high dose group does not cross (is not less than) the non-inferiority margin of 60%. For demographic data and secondary outcome comparisons between the study group continuous variables were summarized as median and interquartile range (IQR) and compared with student t test or Mann Whitney U test as appropriate. Categorical variables were presented as number and percentage, and compared by chi square test. All p values were two sided, and considered statistically significant if less than 0.05, no adjustments were made for multiple testing Statistical analysis was carried out on SPSS-19

RESULTS

The study groups were balanced regarding age (p=0.12) and gender distribution (p=0.15), however, patients in group H had a significantly higher APACHE 4 score (median of 78 Vs median of 63 in group S, p = 0.048), SOFA score medians were equal in both groups at a value of 8 (p=0.17), similarly, Charlson comorbidity index was equal with an insignificant p value of 0.062, however, group H had a higher average baseline heart rate(HR) and lower mean arterial pressure(MAP) (p = 0.006 and 0.042 respectively). S group patients had lower baseline average UOP (median of 1960 Vs 2350 in group H, p = 0.01), and higher serum albumin (p=0.022). There was no significant difference between groups in blood urea and creatinine clearance, as well as bilirubin, platelets, respiratory rate, and body weight. All patients were carbapenem resistant and using Clinical and Laboratory Standards Institute 2009 criteria[25] susceptible to Colistin (minimum inhibitory concentration [MIC] ≤2 mg/L) [Table 2].

Primary outcome: In S group 83 patients (76.15%) did not develop kidney injury, whereas in H group 54 patients

(73.97%) did not develop kidney injury, the 95% confidence interval of the proportion without kidney injury in H group was 63.91–84.04%, the single tailed lower 97.5% CI was higher than the non-inferiority margin of absolute 15 percentage points less than the predefined proportion in the standard dose group. Non inferiority of Colistin high dose is thus established with regards to safety (Fig. 1).

Secondary outcomes: 77 patients in S group (70.6%) were discharged alive, while 51 patients (69.9%) in the H group were discharged alive from the hospital (p = 0.99), the average length of stay (LOS) for group S in ICU and hospital were 15 and 51 days respectively, while for H group they were 10 and 48 days respectively, average LOS in ICU was less than the standard dose and hospital did not differ between groups (p = 0.035 and 0.07 respectively). Median of the duration of therapy in group S was 12 days as compared to 14 days in group H, there was no difference between both groups (p = 0.26), the median cumulative dose of group H (as would be expected) was significantly higher than that of group S, being 102 million units for group H and 57 million units for group S (p < 0.001). In group S 90 patients (82.6%) showed microbiological improvement, whereas 63 patients (88.3%) in group H showed microbiological improvement (p = 0.025), as for clinical improvement 86 patients in group S clinically improved, representing 78.9%, while 51 group H patients clinically improved representing 69.9%, there was no statistically significant difference (p=0.09). Combined clinical and microbiological improvement (global improvement) occurred in 70 patients in group S, and 42 patients in group H, representing 64.2% and 57.5% respectively, p value of 0.06 was insignificant statistically. Table 2 summarizes secondary outcomes (Table 3).

Table-1: High versus standard dose of Colistin

Renal assessment	Group H		Group S	
	Daily Dose (MU)	Frequency	Daily Dose (MU)	Frequency
Normal renal function	9 million IU (240 mg CMS)	Divided into 3 doses per day	6 million IU (480 mg CMS)	Divided three times daily
CrCl 50-89 ml/min OR serum creatinine 1.3–1.5 mg/dl	9 million IU (240 mg CMS)	Divided into 3 doses per day	4 million IU (320 mg CMS)	Divided three times daily
CrCl 10-49 ml/min OR serum Creatinine 1.6–2.5 mg/dl	[(CrCl x 1.5) + 30] / 12	Divided into 3 doses per day	2 million (160 mg CMS)	Every 24 hours
CrCl <10 ml/min OR serum creatinine ≥2.6 mg/dl	[(CrCl x 1.5) + 30] / 12	Every 24 hours	2 million (160 mg CMS)	Every 36 hours

Table 2: Baseline characteristics of study groups

	Standard Dose (109)	High Dose (73)	P value
Age: years median (IQR)	59 (34.25)	52 (24)	0.12
Gender: Male: n (%)	80 (73.4)	61 (83.6)	0.15
Weight (kg) median (IQR)	70 (21)	70 (20.25)	0.5
APACHE IV: median (IQR)	63 (83.5)	78 (32.5)	0.048
SOFA Score median (IQR)	8 (7)	8 (3)	0.17
Charlson Index median (IQR)	5 (7)	5 (5)	0.062
Baseline HR (bpm) median (IQR)	95 (24)	105.5 (17.5)	0.006
Baseline RR (per min.) median (IQR)	26 (5.5)	26.5 (9.75)	0.3
Baseline MAP (mmHg) median (IQR)	79 (13.5)	75 (14)	0.042
Baseline CrCL: ml/min median (IQR)	75 (55)	83 (105.5)	0.122
Baseline UOP: ml/day median (IQR)	1960 (930)	2350 (960.75)	0.01
Baseline Urea: mmol/L median (IQR)	11 (10.65)	10.5 (10.75)	0.946
Baseline Albumin g/dl median (IQR)	23 (3.5)	25 (4)	0.022
Baseline Bilirubin umol/L median (IQR)	10 (11)	12 (10.75)	0.05
Baseline Platelets 10^9/L median (IQR)	268 (209)	323.5 (205)	0.066

IQR = interquartile range, APACHE = Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, bpm = beats per minute, mmHg = millimeter of mercury, mmol = millimole, umol = micromole, MAP = mean arterial pressure, Cr Cl = creatinine clearance

Table 3: Secondary outcomes

Variable	Standard dose (109)	High dose (73)	P value
Hospital outcome: alive n (%)	77 (70.6)	51 (69.9)	0.99
ICU LOS: days median (IQR)	15 (8)	10 (4)	0.035
Hospital LOS: days median (IQR)	51 (42)	48 (31)	0.07
Therapy Duration: Days median (IQR)	12 (6)	14 (6)	0.26
Cumulative Dose: Million Units median (IQR)	57 (46)	102 (52.75)	< 0.001
Microbiological Improvement n (%)	90 (82.6)	63(88.3)	0.025
Clinical Improvement n (%)	86 (78.9)	51 (69.9)	0.09
Global Cure n (%)	70 (64.2)	42 (57.5)	0.06

Fig. 1: 95% CI of Group H patients without kidney injury

DISCUSSION

Choosing an antibiotic is a critical factor in the survival of a critically ill patient because of emerging resistance against many commonly used antibiotics, carbapenem groups for instance. Colistin is considered an effective treatment for CR-GNB. This study therefore, was performed to assess the efficacy of the high dose of Colistin compared to the standard dose with an aim to find an appropriate dosage regimen that can help to optimize its efficacy, safety and reduce the incidence of resistance as well as avoiding kidney injury. in our study all patients were carbapenem resistant and (using Clinical and Laboratory Standards Institute 2009 criteria[19]) susceptible to Colistin (minimum inhibitory concentration [MIC] ≤2 mg/L). This study showed no difference in 14-day mortality between two groups (P=0.99), overall mortality within two groups was 54 (29.6%). In addition, we found no difference in the average LOS for intensive care between the two groups, i.e., 10 days Vs. 11 days respectively, (P=0.39). Similarly, no differences were found in the duration of treatment or microbiological improvement. We, however, noticed a difference in clinical improvement in group S and group H 86% and 51 %, respectively (P=0.09) which is reflected on a global improvement between the two groups (group S 70% versus Group H 42% (P= 0.06). In other studies, similar results were seen. In fact, Cheng et al.'s study had a 70% cure rate[20] and 82.1% for the study of Dalfino et al[21] In a previous study, AKI was reported in 32.2% and 26% of Colistin courses in the high-dose and standard-dose groups, respectively, with no significant difference (p = 0.64). The times before the onset of AKI were similar (a median of 7 and 9.5 days for the high-dose and standard-dose groups, respectively.[22]

We found similar results in the present study, with renal toxicity not statistically significant between the two groups, and consequently, we determined that the high dose of Colistin was not below the standard dose. The difference in outcome was significant in high dose verses standard dose groups. we would however, like to mention that in our hospital the practice was to start standard dose for milder infection while using higher doses of Colistin for patients who had severe infections with risk for treatment failure and co-infections with other organisms. But after the results of this study, we can start the high dose in mild infections. According to these results we recommend the use of target serum concentration equation to find the proper dosage regimen depending on minimum inhibitory concentration (MIC) of bacteria. Even it is well known that Colistin may cause nephrotoxicity but the exact mechanism is unclear. In a review article in 2011 the prevalence of nephrotoxicity varied among trials from 0-53.5%.[23-25] with different risk factors that may have led to increased incidence of nephrotoxicity like duration of therapy, daily dose, concomitant use of other nephrotoxic agents, age, hypoalbuminemia, hyper-bilirubinemia, severity of the patient's illness, underlying disease and male sex.[26,27]

The high-dose Colistin appears to have contributed to a high response rate, raising the Colistin concentration at the infected site. To keep an eye on renal functions and for the titration of Colistin dose in our study we used RIFLE criterion (Risk, Injury, Failure, Loss, End stage renal disease). We can divide the acute deterioration in kidney function on the basis of three parameters of RIFLE criterion three grades (Risk, Injury, and Failure) and two outcomes (Loss and End stage renal disease).and suggest that criteria such criteria may be used to guide its proper dosing, without leading to clinically significant nephrotoxicity. Dealing with severely ill patients has led us to think in a new way to describe the nephrotoxicity related to higher doses of Colistin, where we consider patients according to RIFLE criteria with no acute change in the kidney function or Risk (R) without clinical significance kidney injury due to multiple risk factors plus to high morbidity/mortality of our ICU patients. When we classify nephrotoxicity to significant (I, F, or L) and non-significant (No change or R) results showed non inferiority of high dosing in safety related to kidney.

CONCLUSION

The high dose of Colistin for the treatment of carbapenem resistance gram negative bacilli (CR-GNB) was as safe as the standard dose for renal safety. The other beneficial effects were the early microbial clearance and the shorter span of ICU stay when we used high dose of Colistin

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