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ORIGINAL ARTICLE

Clinical outcomes and safety of colistin in treatment of gram negative infections: A prospective observational study

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KEYWORDS

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Abstract *Background:* Despite the fact that colistin has a significant activity against MDR gram-negative organisms, its toxicity limits its use. However, the limited therapeutic options due to increasing antibiotic resistance have made re-evaluation of older antibiotics inevitable. In contrast, lack of data to guide the usage of these drugs demands for studies on their safety and efficacy. This studies the clinical outcomes and safety of colistin at a tertiary care centre in Mumbai.

Materials and methods: A prospective observational study was conducted at P.D. Hinduja Hospital, Mumbai for a period of seven months. Diagnosis of infection was based on CDC guidelines and APACHE II score was used to assess the severity of illness. Clinical and microbiological response to colistin was evaluated along with the incidence of nephrotoxicity (RIFLE criteria) and neurotoxicity.

Results: Sixty-two patients (median age 56 years, with documented gram negative bacterial infection and mean APACHE II score 22) received colistin. Clinically favourable response was seen in 71% patients. However, the mortality among the study population was 27%. Univariate analysis identified pneumonia and ICU admission as independent factors for adverse outcome. Deterioration of renal function was observed in 35.89% as per RIFLE criteria. 6 (9.6%) patients demonstrated neurotoxicity.

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Conclusion: Colistin is effective in treatment of gram negative infections and its use should be reappraised. However since colistin is the last resort it is imperative to make its best use to ensure that it remains as a safe and effective mode of treatment when need be.

1. Introduction

Colistin, a polymyxin class of antibiotic, was used for about two decades after its discovery in 1950, but the reported nephrotoxicity and neurotoxicity led to a gradual decrease in its use by 1970s [1–3]. Now with the increase in antibiotic resistance and the immediate threat of a decline in the discovery and development of new antibiotics, treatment of serious gram negative infections has almost reached the pre-antibiotic era [4]. Virtually no drugs are available to effectively treat MDR gram-negative pathogens. Thus restricted therapeutic options have made the medical fraternity rekindle interest in colistin; previously discarded due to toxicity and availability of safer and less toxic antibiotics [5]. It has been reported that colistin has significant activity against MDR gram negative pathogens, but the safety and efficacy profile of colistin, to guide its usage is not reported in the Indian population, with limited studies across the globe. Hence, this study was performed to present data regarding the clinical characteristics, and outcome (clinical and microbiological) with emphasis on adverse events (nephrotoxicity and neurotoxicity) of a group of patients with resistant gram-negative infections being treated with colistin.

2. Materials and methods

2.1. Study site and design

The study was conducted at P.D. Hinduja National Hospital and Medical Research Center (PDHNH and MRC), Mahim, Mumbai. It is a tertiary care hospital, with 380 inpatient beds. It was a single-centre, prospective observational study, carried out from June 2010 to January 2011, approved by the Institution Review Board (IRB) of PDHNH and MRC.

2.2. Patient inclusion and exclusion criteria

Inclusion criteria: (a) patients more than 18 years of age admitted to the ICU or wards of the hospital and (b) on intravenous colistin for microbiologically documented gram negative infections for at least 72 h, were included.

Exclusion criteria: (a) pregnant and nursing women and (b) patients infected with micro-organisms resistant to colistin such as, Proteus spp., Serratia spp., Morganella spp. and, (c) patients receiving less than 72 h of treatment with Colistin were excluded.

2.3. Data collection

All patients prescribed colistin were identified prospectively from the hospital pharmacy. A standard case report form was used to capture demographic and hospital admission details, reason for admission and co-morbidities. APACHE II [6] score was calculated at the time of ICU admission and one day before starting colistin to assess the severity of illness. All available culture sensitivity reports, laboratory data, dosage and duration of colistin therapy, simultaneous co-infections, use of other antibiotics and concomitant use of nephrotoxic drugs were documented.

2.4. Definition of infections and outcome

2.4.1. Site of infection

Type of infection was assessed according to US Centers for Disease Control and Prevention (CDC) criteria. Specifically, diagnosis of pneumonia required chest radiographs with at least one of the following: new or progressive and persistent infiltrate, consolidation, cavitation, or pleural effusion. In addition, patients must have had fever >38 °C with no other recognised cause, or abnormal white blood cell count [leucopenia (<4000 WBC/mm^3) or leucocytosis ($\geqslant 12.000$ WBC/mm^3)], and at least two of the following: new onset of purulent sputum or change in character of sputum, increased respiratory secretions or increased suctioning requirements, new onset or worsening of cough or dyspnoea or tachypnea, rales or bronchial breath sounds, or worsening gas exchange [7]. Bacteremia required growth of a recognised pathogen from one or more blood specimen cultures [8]. Infections at other body sites or fluids, such as urinary tract infections and surgical site infections were defined based on guidelines from CDC.

2.4.2. Products administered

Each patient either received, Colomycin; Forest Laboratories, UK or Xylistin; Cipla Pharmaceuticals, India, administered intravenously at a dose of 2 million units three times a day, in most patients with normal renal function. Patients with pre-existing renal insufficiency received colistin dose corrected for their creatinine clearance. Defined Daily Dose (DDD) was calculated for the convenience of comparison of doses used in different patients. No. of DDD = No. of items issued X amount in each vial/WHO DDD measure. WHO DDD measure for parenteral use of colistin is 3 MU [9].

2.4.3. Microbiological testing

Identification of all causative microorganisms was performed by classic microbiologic methods. Susceptibility testing was performed using the Clinical and Laboratory Standards Institute Guidelines (CLSI) 2010 for *Pseudomonas* and *Acinetobacter* spp. [10]. EUCAST criteria were used for Enterobacteriaceae. Bacteria for which MIC to colistin was 2 mg/l or less were considered susceptible while bacteria with MIC 4 mg/l or more were considered resistant. Susceptibility to colistin was tested with the use of 10 μg of colistin disc for Pseudomonas. Isolates were considered sensitive if the inhibition zone was 11 mm or more.

2.5. Final outcome

2.5.1. Microbiological outcome

Bacteriological eradication was defined as, eradication of gram negative isolates on follow up culture, wherever available. *Presumed eradication* was defined as no repeat culture was available and the patient had a favourable clinical response. Presumed non eradication was defined as no repeat culture was available and patient had an unfavourable clinical response. *Persistence* was defined as continued isolation of the gram negative isolate on follow up culture. *Superinfection* was defined as isolation of a same or different gram-negative organism from a different site while on colistin.

2.5.2. Clinical outcome

Favourable response was defined as complete or partial resolution of presenting signs and symptoms. *Unfavourable response* was defined as persistence or worsening of presenting signs and symptoms. *Indeterminate response* was defined as inability to assess clinical response. *Death* was defined as death occurring during colistin treatment [11].

2.5.3. Evaluation of response

All patients were followed up to record the clinical and microbiological outcome at the end of treatment. For nephrotoxicity evaluation, the baseline creatinine and the highest creatinine value during colistin therapy were noted and RIFLE (Risk, Injury, Failure, Loss and End Stage Kidney Disease) criteria were estimated. RIFLE criteria define three grades of severity of AKI (Risk, Injury and Failure) based on changes to serum creatinine and urine output and two clinical outcomes (Loss and End-stage) [12]. In this study we used the creatinine criteria to check for renal function deterioration. The case notes were evaluated for any neurotoxic event independent of the cause. The clinical criteria used in the evaluation included resolution of clinical signs and symptoms, including: Temperature less than 38 °C, White cell range 4×10^9/L–12×10^9/L and confirmation about resolution of signs and symptoms as per the treating consultant.

2.5.4. Statistical analysis

All statistical tests were performed using Stata version 10.1. For qualitative data Chi square test and Fischer's exact test were used for univariate analysis. Mean and standard deviation were calculated for quantitative data. Wilcoxon's rank-sum test was used to compare each variable with outcome individually. A p-value of <0.05 was deemed statistically significant. Variables with $p < 0.2$ in the univariate analysis were considered for inclusion in the multivariate analysis using the multiple forward logistic regression method.

3. Results

3.1. Study population

(Table 1) In total 108 patients were screened from a period of June 2010 to January 2011, of which 62 were included in study (summarised in Fig. 1).

Pseudomonas aeruginosa (41.9%) and *Acinetobacter* spp. (24.2%) were the most common causative organisms, followed by *Klebsiella pneumoniae* (16%). Colistin was most commonly prescribed for pneumonia (27%) followed by other lower respiratory tract infection (18%) and UTI (18%), bacteremia (16%) and surgical site infection (13%). 74% of all the isolates were resistant to other antibiotics and patients received monotherapy with colistin. The mean DDD of colistin in patients with normal baseline creatinine was 16 (±8.65) and 11 (±9.5) in patients with high baseline creatinine. The average no. of days of therapy with colistin was 11 ± 5.4 days.

3.2. Clinical and microbiological outcome

A clinically favourable response was seen in 44 (71%) out of 62 patients, clinical assessment was not possible in 1 and there were 17 (27%) deaths while the patients were on colistin. Of the 44 patients with a clinically favourable response 30 were categorised as presumed eradication, 7 were documented eradication, 5 with persistent infection and 2 were super infection.

Mean duration for mortality from starting colistin was 7 days; cause of death in 12 patients was septic shock with multi-organ failure (MOF), sepsis in 3 patients, severe sepsis in 1 and MOF with pneumonia in one patient.

Microbiological response was evaluated in 48 patients; 63% had presumed eradication, 15% had eradication of gram negative isolates, 10% showed persistence and 12% had superinfection. 14 patients categorised as presumed non eradication had died due to ongoing infection.

ICU admission and pneumonia were independent factors; significant for adverse outcome in the univariate analysis (Table 2). Male gender, ICU admissions, APACHE II score 1 day prior to starting colistin, pneumonia and number of DDDs of colistin administered were controlled for in the multivariate analysis. However, no factor was found to be statistically significant in the multivariate analysis (Table 3).

Table 1 Demographic and clinical Characteristic for patients enrolled in the studied.

Characteristic	Values (n = 62)
Age (years) (median, range)	56 (18–92)
Male gender [n (%)]	44 (71)
ICU admission [n (%)]	41 (66)
APACHE II score one day prior to staring colistin (mean ± SD)	22 ± 8
Underlying condition (%)	
None	21
Hypertension	12
Diabetes mellitus	04
HTN + DM	08
Respiratory	07
Malignancy	07
Cardiac	03
Multiple	37
Total hospital stay (mean ± SD)	35 ± 29
Day in hospital until 1st day of colistin (mean ± SD)	11 ± 8.5

Total no. of patients screened 108

↓

Total no. of patients eligible – 74

↓

Total no. of patients included in the study 62

Figure 1 Patient accountability chart.

3.3. Nephrotoxicity

Total 39 patients were evaluated for nephrotoxicity (17 patients were excluded due to death, 5 were excluded as they were receiving renal replacement therapy prior to starting colistin and one was excluded as the patient was transferred to another hospital). 25 patients had normal baseline creatinine and 14 had a high baseline creatinine. Fig. 2 gives classification of patients based on RIFLE criteria. Incidence of nephrotoxicity as per RIFLE criteria was found to be 35.89% and the incidence of Acute Kidney Injury (AKI) and Acute Renal Failure was found to be 15.38%. No significant predictor of nephrotoxicity was found in the univariate analysis (Table 4).

3.4. Neurotoxicity

Six patients (9.6%) showed neurotoxicity in the form of focal seizures not attributable to other identifiable cause.

4. Discussion

This study reveals prospective observational experience with the use of colistin, a cationic polypeptide antibiotic of the polymyxin family that is rapidly bactericidal to Gram negative bacteria.

The study enrolled total of 62 patients included in the analysis. A clinically favourable response was seen in 71% patients. This is in keeping with previous studies that have confirmed efficacy of colistin in the treatment of Gram-negative bacterial infections between 45% and 88% [13–18].

A retrospective study performed on cohort of patients treated with colistin for microbiologically documented infections in 258 patients has been reported [19]. In this study, a clinical cure rate of 83.3% was observed in patients treated with colistin monotherapy or colistin combined with meropenem. The presence of malignancy and infections other than pneumonia were independent risk factors for failure to cure the infection. In another study, it was found that the severity of illness (APACHE II score) was the only significant predictor of

Table 2 Univariate analysis of factors associated with adverse outcome.

Characteristic	Favourable response (n = 44)	Death (n = 17)	P-value
Age (years) (mean ± SD)	57 ± 20	55 ± 15	0.717
Male gender [n (%)]	34 (77)	09 (52)	0.061
ICU admission [n (%)]	24 (54.55)	16 (94)	0.0035
APACHE II score at ICU admission (mean ± SD)	19.33 ± 8.46	21 ± 8.35	0.376
APACHE II score 1 day prior to starting colistin (mean ± SD)	20.58 ± 8.4	24.31 ± 7	0.074
No. of Defined Daily Doses (mean ± SD)	15 ± 9.97	10 ± 5.4	0.06
Underlying disease [n (%)]			
Hypertension	5 (11.36)	2 (11.76)	0.964
Diabetes mellitus	3 (6.8)	0	
HTN + DM	4 (9.09)	0	
Respiratory	2 (4.54)	2 (11.8)	0.308
Cardiac	1 (2.72)	1 (5.9)	0.483
Malignancy	3 (6.8)	1 (5.9)	1
Multiple	16 (36.36)	7 (41.1)	0.728
Others	1 (22.72)	0	
Length of hospital stay (days) (mean ± SD)	39 ± 32.06	23 ± 14.9	0.019
Duration of hospitalisation until 1st day of colistin treatment (days) (mean ± SD)	10 ± 7.5	15 ± 10.19	0.083
Responsible pathogen [n (%)]			
Pseudomonas aeruginosa	18 (40.9)	8 (47.2)	0.663
Acinetobacter spp.	12 (27.27)	3 (17.6)	0.433
Klebsiella pneumoniae	7 (15.9)	3 (17.6)	0.869
Polymicrobial	4 (9.09)	0	
Others	3 (6.8)	3 (17.6)	0.202
Condition treated [n (%)]			
Bacteremia	7 (15.9)	2 (11.6)	0.6824
Pneumonia	9 (20.45)	8 (47.05)	0.037
LRTI	9 (20.45)	2 (11.76)	0.428
UTI	9 (20.45)	2 (11.76)	0.428
SSI	7 (15.9)	0	
Others	3 (6.8)	2 (11.76)	0.612

Table 3 Multivariate analysis of risk factors associated with adverse outcome OR, Odds Ratio; CI, Confidence Interval.

Risk factor	OR (95% CI)	*P*-value
Male gender	0.439 (0.10–1.85)	0.263
ICU admission	3.498 (0.13–89.29	0.449
Pneumonia	0.287 (0.06–1.35)	0.116
APACHE II score one day prior to starting colistin	0.96 (0.87–1.05)	0.408
DDD	1.115 (0.99–1.24)	0.057

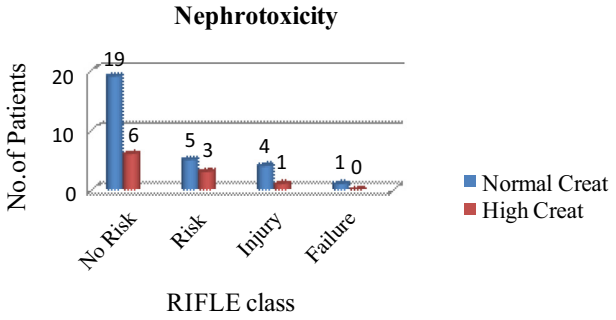

Figure 2 Incidence of nephrotoxicity using RIFLE criteria.

clinical response to colistin [20]. However, univariate analysis in our study identified pneumonia and admission to the ICU as independent risk factors for adverse outcome, and efficacy of colistin did not differ against a particular organism. These risk factors were not found to be significant on multivariate analysis.

Nephrotoxicity is an important adverse effect of colistin treatment and renal function should be closely monitored. Deterioration of renal function could be a part of the ongoing sepsis and multi-organ failure; hence patients with death as the outcome were excluded from evaluation of nephrotoxicity. Incidence of nephrotoxicity reported in literature is 9–56% [21–24]. The occurrence of AKI and ARF was relatively lower (15.38%) in this study compared to other studies. No factor was found to be a significant predictor of nephrotoxicity in this study, which could be due to the small sample size. None of the patients showing AKI or ARF required initiation of haemodialysis.

The incidence of neurotoxicity was found to be 9.6%. Of the 6 patients, 2 were on combination treatment with carbapenems (doripenem and meropenem), which have a low incidence of neurotoxicity. One patient had an underlying CNS malignancy and one was admitted with diffuse axonal head injury both of which can independently cause seizures. In studies by Cheng et al. and Holloway et al., 3.5% neurotoxicity was reported.

In our study, all 6 patients showing neurotoxicity had accompanying nephrotoxicity; consistent with that reported by Sabuda et al. where 4 instances of neurotoxicity (numbness, muscle weakness and tingling) were reported and all four had impaired renal function.

Each study has its pros and cons due to the ethical and practicability issues. In this study the prospective nature of the study allowed inclusion of cases with a confirmed clinical infection, eliminating the drawback with retrospective studies. However, this study was not designed to particularly investigate the effectiveness of colistin, in comparison to a control group. Due to the small sample size no correlation could be made with respect to the dosing regimen used and the outcomes. The use of RIFLE criteria gives a better insight into the incidence of nephrotoxicity. Despite some of the limitations of the study, we believe the results of the study may be useful to clinicians and researchers as this is the first study carried out in India on safety and efficacy of colistin.

5. Conclusion

Though the data presented in this study are for a very small patient pool, they prove that colistin is effective in the treatment of gram negative infections. The occurrence of toxicity is at an acceptable level. Thus, the benefits outweigh the risk factors associated with the use of colistin. Colistin should be used as a reserve drug to treat patients with carbapenem-resistant gram negative infections. Hence, it is necessary to monitor the use of colistin such that this resource should be used judiciously and reserved as the last bastion in the

Table 4 Univariate analysis of risk factors in patients with and without nephrotoxicity.

Parameter	Patients with nephrotoxicity (n = 14)	Patients without nephrotoxicity (n = 25)	*P*-value
Age (years) (mean ± SD)	65 ± 18.46	57 ± 19.09	0.159
DDD (mean ± SD)	17 ± 9.5	15 ± 10.71	0.411
Duration of colistin therapy (days) (mean ± SD)	12 ± 6.45	10 ± 5.01	0.452
APACHE II score 1 day prior to starting colistin (mean ± SD)	20 ± 6.3	18 ± 7.7	0.605
Co-administration of nephrotoxic drugs [n (%)]	11 (78)	17 (68)	0.481
Underlying disease [n (%)]			
DM	2 (14.28)	1 (4)	0.289
HTN	1 (7.14)	3 (12)	1
DM + HTN	1 (7.14)	3 (12)	1
Respiratory	0	2 (8)	
Cardiac	0	1 (4)	
Cancer	1 (7.14)	2 (8)	1
Multiple	6 (42.85)	8 (32)	0.497
Others	0	1 (4)	

treatment of serious infections. It is thus imperative to make the best use of colistin to ensure that it remains as a safe and effective mode of treatment when need be.

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Competing interest

None to declare.

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