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Original Research Article

Safety and effectiveness of colistin compared with non-colistin combinations in the treatment of multi drug resistant bacterial infections

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ABSTRACT

Background: Multi drug resistant (MDR) bacteria are usually defined as when it is resistant to three or more group of antibiotics. The objective of this study was to determine the efficacy and safety of colistin when compared with other antibiotics for the treatment of infections caused by MDR *Acinetobacter baumannii* and *Pseudomonas aeruginosa.*

Methods: A single centre, prospective cohort study was conducted at Krishna Institute of medical Sciences, Hyderabad, India between September 2016 to March 2017. Seventy-four patients (74) were included in the study. Primary outcome were good clinical response and thirty days' mortality, secondary outcome were microbiological response and adverse drug reactions of the drug.

Results: A total of 74 patients were enrolled into the study. Forty patients (40) were received intravenous colistin dose of 2.5mg-5mg/kg/day. Remaining thirty-four patients (34) received other antibiotics which includes carbapenem, aminoglycosides. etc. The mean age, gender, underlying conditions and severity of illness of the patients in both groups were significantly same. In colistin group 27 (67.5%) patients and 11 (32.3%) patients had good clinical response. The overall mortality of the patients in the colistin group was 17.5% and that in the non-colistin group was 38.2%. The incidence of nephrotoxicity in colistin was 15% and 35.2% in non colistin group. No neurotoxicity was observed in present study.

Conclusions: Our study concludes treatment with colistin decreases patient mortality and increase the clinical response in multidrug-resistant *A. baumannii* and *P. aeruginosa* infected patients. However large multicentric clinical trials are needed to demonstrate the safety and efficacy of colistin.

Keywords: *Acinetobacter baumannii,* Colistin, Multi drug resistant, Nephrotoxicity, *Pseudomonas aeruginosa*

INTRODUCTION

The emergence of multidrug-resistant (MDR) gram-negative organisms (GNB) causing nosocomial infections is a growing problem worldwide.[1] MDR bacteria are usually resistant to three or more group of antibiotics. *Acinetobacter baumannii, Pseudomonas aeruginosa* are the main MDR-GNB producing serious infections. The treatment of these infections is difficult due to the lack of active antimicrobials.[2,3] It has emerged as one among the most significant nosocomial pathogens in health-care setting. Carbapenems were one of the most active agents against *A. baumannii, P. aeruginosa* but due to the overuse of these drugs, carbapenem-resistant strains have rapidly emerged during the last decade this has led to a renewed interest in antibiotics like Colistimethate sodium, which were abandoned in 1980s because of nephrotoxicity and neurotoxicity.[4] Over the past few years there have been reports of treating patients infected with MDR *A. baumannii* and *P. aeruginosa* with polymyxin B and colistin.[5,6]

Colistin belongs to the polymyxin class of cationic polypeptide antibiotics. It is administered as the prodrug

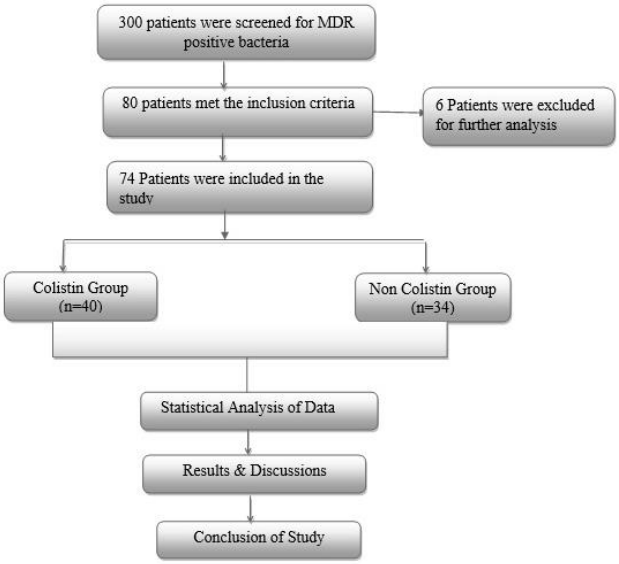
colistimethate sodium (CMS), a fraction of which is hydrolyzed in vivo to colistin.[7] Since its recent reemergence, data suggest that colistin is associated with a much lower rate of renal toxicity compared with historical reports.

The majority of recent studies report toxicity rates of 10%-30%.[8] However, only a few studies were comparative and these lacked the sample size needed to compare colistin versus state-of-the-art antibiotics.

The objective of this study was to determine the efficacy and safety of colistin when compared with other antibiotics for the treatment of infections caused by MDR *A. baumannii, P. aeruginosa*.

METHODS

This is single centre, prospective cohort study was conducted at Krishna Institute of medical Sciences, Hyderabad, India between September 2016 to March 2017. This study was approved by hospital Ethical Committee (EC). During this study period, almost 300 patients were screened, 74 patients were included into the present study (Figure 1).



Excluded: Six patients were excluded from study; three received very high dose of colistin, two patients were died after 2 days' administration of antibiotics, one because patient's incomplete data were available

Figure 1: Study flow diagram.

The eligible subjects were hospitalized patients with over the age of 18 years who were infected with *A. baumannii* or *P.aeruginosa* resistant to beta-lactams, fluoroquinolones and aminoglycosides. Patients were evaluated at the beginning of treatment for the following data: age, gender, identification of pathogen, and severity of clinical condition according to the Acute Physiological and Chronic with a Goof Outcome Health Evaluations II (APACHE II) scoring system. Patients were followed up until the end of the treatment for outcome that was considered improved or deteriorated based on clinical criteria.

Colistin was offered to all MDR infectious patients. The choice of the treatment depends on the attending physician. If the Attending physician agreed to have colistin treatment, the patients received intravenous colisitn treatment ranging from 2.5-5mg/day in two divided doses categorized as colistin group. Remaining patients who were treated with other antibiotics. i.e. aminoglycosides, beta lactams, macrolides, and tetracyclines considered as non colistin group.

All isolates of *A. baumannii and P. aeruginosa* from the eligible patients were tested for colistin susceptibility done according to an automated method (bioMerieux Vitek, Hazelwood, MO); susceptibility to various (gram-negative susceptibility cards PA and GD). Susceptibility to colistin was tested by Disk Diffusion methods according to the manufacturer's guidelines.

Inoculum were prepared by suspending colonies from overnight sample agar plates in sterile saline to the turbidity of a 0.5 McFarland standard. Colistin containing 10µg disks were dispensed onto the surfaces of Mueller-Hinton inoculated agar plates and incubated at 35°C for 16 to 18 h. Quality control strains of *Escherichia coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were used with the reference MIC range of 0.5-1 and 0.5-2 mg/l, respectively. All Isolates were considered as susceptible if the inhibition zone was >11 mm.

The Primary outcomes were Good clinical response and 30 days' mortality. A good clinical response referred to a combination of clinical cure and clinical improvement. Secondary outcome were Nephrotoxicity, Neurotoxicity and Microbiological response. Good Microbiological response was defined as complete eradication of organism from the patient body at the end of the treatment.

RESULTS

Between September 2016 to March 2017, eighty (80) patients had positive culture report during study period.

Six patients were excluded from further analyses; three patients received very high dose of colistin, 2 patients were died after 2 days' administration of antibiotics, one because patient's incomplete data were available. A total of 74 patients were included in the present study.

Forty patients were in the colistin group and thirty-four patients in the non-colistin group. The baseline characteristics of the patients are shown in Table 1. The mean age, gender, severity of illness of the patients in both groups was significantly same. In the colistin group, 16 patients (40%) were infected with *A. baumannii* and 26 patients (60%) were infected with *P. aeruginosa,*

whereas 27 patients (79.4%) were infected with *A. baumannii* and 7 (20.5%) were infected with *P. aeruginosa* in the non-colistin group.

Table 1: Baseline characters of study subjects.

Character	Colistin	Non-colisitn
Male	32(80%)	23(67.64%)
Female	8(20%)	11(32.3)
Mean Age	54.02	55
ICU Admission	100%	100%
Ventilations	14(35%)	14(41.7%)
Mean APACHE II Score	28.7	28.9
Pre-existing renal impairment	5(12.5%)	4(11.7%)
Acinetobacter baumannii	16(40%)	79.4(27%)
Psuedomonas aeruginosa	26(60%)	7(20.58%)

In-vitro colistin susceptibility testing was determined by disk diffusion test. This test revealed all *A. baumannii* and *P. aeruginosa* isolates had a MIC of colistin less than 2 mg/l and were considered susceptible to colistin.

Table 2: Underlying conditions.

Condition	Colisitn	Non-colistin
Cardiovascular problems	2(5%)	1(2.9%)
Traumatic Injury	3(7.5%)	6(17.6%)
Leukaemia	2(5%)	0
Chronic Kidney disease	3(7.5%)	1(2.9%)
Immune suppression therapy	2(5%)	1(2.9%)
Respiratory Problems	5(12.5%)	3(8.8%)
Neurological Problems	5(12.5%)	5(14.7%)
Severe Sepsis	5(12.5)	8(23.5%)
Gastrointestinal Problems	4(10%)	2(5.8)
Comorbidities		
Diabetes mellitus	13(32.5%)	9(22.5%)
Hypertension	17(42.5%)	14(35%)
Hypothyroidism	2(5%)	1(2.5%)

Table 3: Treatment outcome index.

Outcome	Colistin group	Non colistin	p*Value
Clinical response	27(67.5%)	11(32.3%)	0.001
Mortality after 15days of therapy	7(17.5%)	13(38.2%)	0.046
Microbiological response	29(72.5%)	9(26.4%)	0.001
Nephrotoxicity	6(15%)	12(35.2%)	0.04
Neurotoxicity	0	0	-

The choice of treatment purely depends on the treating physician. In colistin group 13 patients (32.5%) received colistin alone, whereas 27 patients (67.5%) received colistin with other antibiotics including vancomycin, carbapenems, aminoglycosides, fluoroquinolones. In non colistin group 3 (8.8%) patients received carbapenem alone, whereas 18 (52.9%) patients received carbapenem with other class of antibiotics, 2 (5.8%) patients received cephalosporin's, 3 (8.8%) patients received penicillin's, 5 (14.7%) patients received vancomycin and 3 (8.8%) patients received aminoglycosides.

The treatment outcomes are shown in Table 3. Twenty-seven patients (67.5%) in colistin group had good clinical response. The clinical response in the patients who received colistin alone was 84.6% and in those who received colistin with other antibiotics was 63%. In non colistin group eleven patients (32.3%) were responded.

Mortality within 30 days was observed in seven patients (17.5%) in colistin group and thirteen patients (38.2%) in non colisitn group (p=0.046). The mortality rate in non colistin group were significantly higher compared to colistin group. There was significant difference in mortality rate described by Kaplan-Meier survival analysis (log rank p = 0.04) (Figure 2).

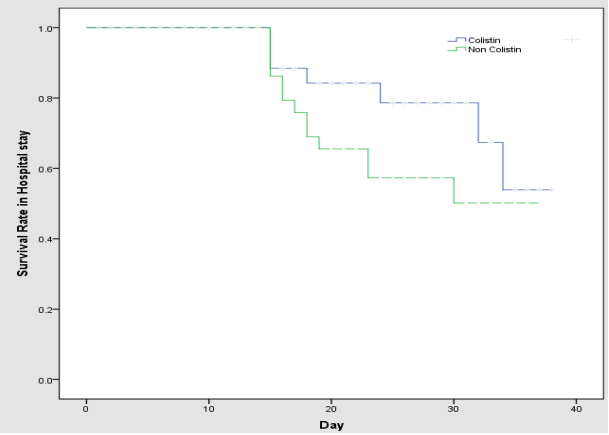


Figure 2: Kaplan-Meier survival curve.

The relative risk of death in the colistin group was 0.45 of the non-colistin group (95% CI 0.206-1.95). The difference in mortality was statistically significant and the number needed to treat (NNT) was approximately five, which implies that only five patients infected with MDR *A. baumannii* or *P. aeruginosa* needed to be treated with colistin in order to prevent one additional death. Bacteriological eradication was observed in 29 (72.5%) of patients treated with colistin and 9 (26.4%) treated with non colistin group (p = 0.001). The median length of total hospital stay after initiation of the antimicrobial was 24 days in the colistin group and 23 day in the non colistin group. In our study, we also measured the incidence of nephrotoxicity. Nephrotoxicity was observed by change in the creatinine and blood urea nitrogen values (Table 4) The rate of nephrotoxicity in both groups were six patients (15%) and twelve (35.2%) respectively.

The incidence of nephrotoxicity is significantly (0.04) higher in non colisitn compared to colistin group. However, five patinets (12.5%) in colisitn group and four

patients (11.7%) in colisitn group had a preexisting renal impairment like patient with chronic kidney injury, patients on Hemodialysis, Kidney transplant patient and nephrectomy. In this study, no neurotoxicity was observed and majority of patients admitted for neurological problem, it's difficult to assess the neurotoxicity associated with drugs. Average dose of colistin is 254mg/day and the average duration of treatment with colistin was 18.3 days.

Table 4: Biochemical characteristics of study subjects.

Parameter	Colistin mean (SD)		Non colisitn mean (SD)		p* Value
	Pre-therapy	Post-therapy	Pre-therapy	Post-therapy	
Serum Creatinine	1.32(1.41)	1.68(1.49)	1.31(1.0)	2.35(1.62)	0.06
Blood Urea Nitrogen	54.58(45.4)	51.5(34.4)	48.1(45.7)	86.2(87.4)	0.02
Platelets count	1.67(1.23)	2.33(1.36)	1.9(1.0)	2.17(1.47)	>0.05

DISCUSSION

In the present study, we evaluated the effectiveness and safety of colistin compared with other antimicrobials agents in patients infected with MDR *A. baumanni* and *P. aeruginosa*.

Our study suggests that treatment of *A. boumanni* and *P. aeruginosa* bacteraemia with colisitn had good clinical response, as demonstrated by lower hospital mortality, compared with other antimicrobial agents. We found significant differences in ICU survival, time to microbiological clearance and elevations in serum creatinine between the colistin and non colistin groups.

Colistin (or polymyxin E) is an old antibiotic discovered from different species of *Bacillus polymyxa* in the decade of 1940s and was extensively used parenterally for more two decades. Subsequently, polymyxins were gradually withdrawn from clinical practice for many years owing to reports of nephrotoxicity and neurotoxicity.[9,10]

In-vitro colistin has a broad spectrum of action against Gram-negative aerobic bacilli, including some strains resistant to carbapenems, aminoglycosides, penicillins, cephalosporins and fluoroquinolones. However, *Proteus mirabilis*, *Providencia spp*., *Serratia spp*., *Morganella morgannii*, *Burkholderia cepacia* and *Stenotrophomonas maltophilia* are naturally resistant to colistin.

The overall mortality in the non-colistin group in this study was was 38.2% which was similar to study conducted by koomanachai in Thailand.[11] Microbiological response was 72.5% in colisitn group significantly higher in compared to non colisitin 26.4%. Two patients in showed good clinical response even without microbiological response. In our study, we excluded patients infected with *A. baumannii* and *P. aeruginosa* with other bacterial infections. Therefore efficacy of colistin on mixed infections was unknown.

Nephrotoxicity was main adverse drug reaction associated with colistin. In the present the incidence of nephrotoxicity in colistin was 15% and 35.2% in non colisitn group. The incidence of nephrotoxicity of the patients in the non-colistin group was significantly more than that in the colistin group. Results of Nephrotoxicity was similar to the recent studies on colsitin.[12,13] Neurotoxicity related to colistin was suspected in two patients in the present study.

However, colistin related weakness may be difficult to discern in critically ill patients and in patients who are receiving parenteral sedatives and neuromuscular relaxants. Larger controlled trials are needed to study the safety of colistimethate sodium, particularly in the setting of multi organ dysfunction. The dose of colistin used in this study was chosen based on FDA guidelines. The main limitation of our study was limited number of patient.

CONCLUSION

Our study concludes treatment with colistin decreases patient mortality and increase the clinical response in multidrug-resistant *A. baumannii* and *P. aeruginosa* infected patients. However large multicentric clinical trials are needed to demonstrate the safety and efficacy of colistin.

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