Effectiveness and Safety of Colistin in Multi Drug Resistant Urinary Tract Infections

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ABSTRACT

Colistin methanesulphonate is an inactive prodrug of which only 30% is converted to the active metabolite, colistin, in the blood and the remaining drug gets excreted unchanged in the urine. The active metabolite is eliminated through non-renal mechanisms. Hence its effectiveness in urinary tract infections (UTI) can be dubious due to the notion that no active metabolite is excreted into the bladder. But colistin has been used in clinical practice for various infections, including UTI, caused by multi drug resistant (MDR) bacteria and there is scarcity of specific reports on effectiveness of colistin in UTI. Hence the objective of our study was to evaluate the effectiveness and safety of colistin in UTI patients admitted to a tertiary care hospital. A prospective observational study was conducted on patients being treated with colistin for UTI. Safety of colistin was evaluated by assessing the causality of adverse dug reactions using Naranjo ADR probability scale and by the RIFLE criteria for severity of acute kidney injury. Clinical outcome was evaluated for each patient on completion of colistin therapy. A total of 80 patients received colistin therapy for UTI and 81% of the UTI were nosocomial. Fifty percent of UTI were relapses and urine cultures identified *Klebsiella pneumonia*e, *Pseudomonas aeruginosa* and *Escherichia coli* as the causative organisms, all of which were MDR. Though colistin dosages were adjusted as per creatinine clearance 36.3% of patients experienced nephrotoxicity. Clinical cure was obtained in 80% of UTI cases. Colistin is effective for treatment of UTI caused by MDR gram negative bacteria but colistin should be used judiciously due to its potential to cause nephrotoxicity.

INTRODUCTION

Polymyxins, isolated from *Bacillus colistinus* in the year 1949, were introduced more than 50 years ago for treatment of infections caused by gram negative bacteria (Kasiakou *et al*., 2005). Polymixins represent a group of five different polypeptide antibiotics (polymyxins A, B, C, D, and E) but only polymixin B and polymixin E (colistin) are used in clinical practice. Colistin sulphate was used orally for the treatment of infectious diarrhoea and bowl decontamination and colistimethate sodium (CMS) was used via parenteral and inhalation routes (Falagas *et al.,* 2005). The use of CMS later declined due to concerns of nephrotoxicity. The emergence of multi drug resistant (MDR) gram negative bacteria and the non availability of new drugs to eradicate them, forced the clinicians to start using the reserved antibiotics such as colistin. CMS is an inactive prodrug which after intravenous administration, is converted to the active metabolite, colistin, in the blood to exert its pharmacological action. But only a small proportion (30%) of CMS is converted (Zavascki *et al.*, 2013) to colistin *in vivo*. The unconverted CMS is eliminated by the kidneys via tubular secretion while the formed colistin is eliminated by non renal mechanisms (Kift *et al*., 2014)**.** Hence its effectiveness in urinary tract infections (UTI) can be dubious due to the notion that no active metabolite is excreted into the bladder. But colistin has been used in clinical practice for various infections, including UTI, caused by multi drug resistant (MDR) bacteria.

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A previous report (Kasiakou *et al.*, 2005) on use of colistin as part of combination therapy for management of various infections due to MDR gram negative bacteria in a cohort of 50 patients found that clinical cure was achieved in 6/6 (100 %) of the UTI treated. But an observational study from Israel (Paul et al., 2010) found colistin to be less effective and more toxic than beta-lactam antibiotics and associated with poor survival in patients with a variety of microbiologically documented pneumonia, UTI, surgical site infection, meningitis or bacteraemia. But specific reports on assessment of effectiveness and safety of colistin for treatment of UTI are scarce in the literature. Hence the objective of the present study was to evaluate the safety and effectiveness of colistin for UTI in patients admitted to a tertiary care hospital.

MATERIALS AND METHODS

A prospective observational cohort study was conducted in a tertiary care hospital (Amrita Institute of Medical Sciences) located in Kochi, Kerala, India after obtaining ethical clearance from the hospital Institutional Review Board. The study period was from October 2014 to May 2015. Daily census of patients receiving colistin was obtained from the pharmacy consumption report through digital hospital information system. All adult inpatients diagnosed with UTI and started treatments with colistin were included in the study. The patients should have their baseline serum creatinine levels measured prior to initiation of colistin. Patients receiving colistin for indications other than UTI and patients on dialysis were excluded from the study. Patients who were discharged against medical advice and patients/or caregivers not willing to sign informed consent were also excluded. UTI was diagnosed based on detection of pathogen in the mid stream urine sample ($>10^5$ colony forming units/ml) in presence of clinical symptoms (dysuria, increased frequency of urination, urgency, new incontinence and/or suprapubic pain/tenderness). Data collected included clinical signs and symptoms of UTI and elevation of lab parameters indicating possibility of infection and inflammation (temperature, WBC, and CRP). Culture and sensitivity (C/s) reports indicating UTI with causative organisms sensitive only to colistin and resistant to all other tested antibiotics resulted in colistin therapy in majority of patients as per hospital antibiotic policy. A detailed examination of the patients' medical records was conducted to gather information on patient demographics, co-morbidities, type of UTI, dose and duration of colistin and other antibiotics administered, concurrent use of potentially nephrotoxic drugs or radio contrast media and occurrence of adverse drug reactions (ADRs) and laboratory parameters including periodic serum creatinine levels and C/s reports. Urine culture was undertaken at the hospital microbiological laboratory by trained staff. A sterile loop delivering 0.001 ml urine was used to inoculate MacConkey and blood agar media and it was incubated overnight at 35 °C in air. The number of colony-forming units (CFU) of each colony type was counted and categorised as $<10^4$, 10^4–10^5 and $>10^5$ CFU/ml. A

single organism at $>10^5$ CFU/ml was classified as 'significant growth' where as a single organism at $<10^4$ CFU/ml or two organisms at $<10^5$ CFU/ml was classified as 'no significant growth'. Cultures growing three or more organisms were reported as mixed growth. All significant organisms were identified and antimicrobial susceptibility testing was performed, where appropriate, using VITEK 2 system (BioMerieux, Marcy I' Etoile, France). Colistin susceptibility was determined using Clinical and Laboratory Standards Institute breakpoints for pseudomonas and acinetobacter species (Clinical and Laboratory Standards Institute 2012). Susceptibility to colistin and polymyxin B for E. coli and Klebsiella spp. were determined using breakpoints (>2mg/L resistant; and ≤2mg/L susceptible) recommended by EUCAST (European Committee on Antimicrobial Susceptibility Testing 2014).

Multi drug resistance was defined as resistance to at least three of five classes of antibiotics which included penicillins, cephalosporins fluoroquinolones, carbapenems and aminoglycosides. The maintenance dose of colistin was adjusted as per calculated creatinine clearance based on Cockcroft-Gault equation (Cockcroft and Gault, 1976). The clinical outcome of each patient after completion of colistin therapy for UTI was described as either a favourable or unfavourable outcome (Sabuda *et al.*, 2012). A favourable outcome was based on one or more of the following such as resolution of clinical signs and symptoms of urinary tract infections, decreasing trends of elevated temperature, WBC and CRP in addition to evidence of microbiological eradication. Unfavourable outcomes included one or more factors such as death during therapy, incomplete duration of colistin therapy and lack of microbiological eradication (culture reports, after completion of colistin therapy, showing the growth of the same organisms which were present initially in the urine sample).

Safety of colistin was assessed by monitoring the adverse drug reactions (ADRs) that may occur with colistin. Patients were continuously monitored for ADRs including nephrotoxicity, neurotoxicity and/or hypersensitivity reactions. Patients were watched for signs of neurotoxicity such as paresthesias, dizziness, and confusion. Signs such as chest tightness and breathing difficulty were also monitored. Patients were also observed for signs of hypersensitivity reactions such as facial edema, swollen tongue, rashes, and urticaria. Cusality of ADRs was evaluated using Naranjo ADR probability scale (Naranjo *et al.*, 1981). Renal function tests, including serum urea and serum creatinine (SCR) levels were measured prior to starting colistin and continuously monitored throughout the duration of colistin therapy and also on first revisit where possible. Nephrotoxicity was defined as at least two consecutive SCR measurements with an increase of 0.5 mg/dl from baseline at least 24 hours apart after two or more days of colistin therapy (DeRyke *et al.*, 2010). In patients with pre-existing renal dysfunction, renal failure was defined as an increase of SCR level ≥ 50 % compared with baseline value. The RIFLE (Risk - Injury -Failure - Loss - End stage renal disease) criteria were used to evaluate the severity of acute kidney injury (Kellum et *al.,* 2008). One million units (MU) of CMS were considered to be

equivalent to 80 mg of CMS or 30 mg of colistin base activity. Colistin consumption was calculated to defined daily dose (DDD) of 3 MU as per the anatomic therapeutic chemical/DDD index from the WHO collaborating centre for drug statistics methodology (WHO Collaborating Centre for Drug Statistics Methodology 2012). Quantitative descriptive analysis was performed using IBM Statistical Package for Social Science (version 20) software for Windows using univariate statistics to report means and standard deviation.

RESULTS AND DISCUSSION

Out of a total of 290 patients who received colistin during the study period for various indications, colistin therapy was evaluated for UTI in 80 patients. The clinical and demographic features of the UTI patients are given in Table 1. Forty four patients (55%) were > 60 years of age, followed by 27 (34%) patients in the age group 41-60 years, and 9 (11%) patients < 40 years of age. These patients belonged to 12 different specialties, general medicine (28, 35%) ranked first, followed by urology and neurology (11, 13.8% each). Twenty one (26%) patients were from the surgical departments and 59 (74%) from medical departments. Co- morbidities commonly observed in the study patients were systemic hypertension and type II diabetes mellitus. Many patients had more than one comorbid condition (Table 1).

Table 1: Clinical and demographic features of UTI patients (n=80).

| Characteristics	Mean ± SD (range) or n (%)
Demographics	
Age	59.5 ± 15.6 yrs (range 19-83 yrs),
Males	47 (59%)
Comorbidities	
Type II diabetes mellitus	39 (48.75)
Hypothyroidism	11 (13.75)
Asthma	06 (7.5)
Dyslipidemia	15 (18.75)
Systemic hypertension	42 (52.5)
Chronic liver disease	08 (10)
Renal failure	14 (17.5)
Prior antibiotic therapy	80 (100)

Out of the 80 patients diagnosed with UTI, majority (65, 81%) were having nosocomial UTI while 15 (19%) patients had community acquired UTI. Out of the 65 patients who had nosocomial UTI, 58 were assessed to have infections acquired from other local hospitals and then transferred to our facility for further management. Majority of the UTI (40, 50%) were due to re-infection (Figure 1). Eleven patients (13.75%) were treated empirically while 69 (86.25%) were treated as definitive therapy supported by culture reports. Colistin was used as a combination therapy with meropenem in 72 (90%) patients and the remaining patients received colistin in combination with other broad spectrum antibiotics. The mean daily dose of colistin was 2 MU±1MU (median = 2 MU, range = 1 to 9 MU) and the mean duration of therapy was 11.41 ± 1.4 days (median = 10 days, range = 3 to 14 days). The average creatinine clearance of all patients was 52 ml/min (range = 14.55 – 129.62 ml/min). Colistin was

administered as a 100 ml infusion in normal saline over 30 minutes. The consumption of colistin during our study period was estimated to be 649 DDDs.
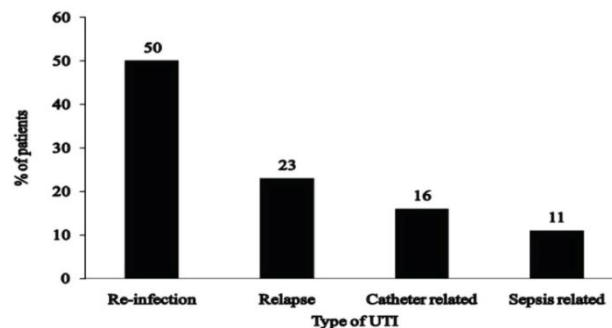
**Fig. 1:** Types of UTI treated with colistin.

Culture reports of urine isolates showed gram negative organisms sensitive only to colistin and resistant to all other antibiotics tested for susceptibility. The top three MDR organisms isolated were *K. pneumoniae* (53 isolates), *E. coli* (17 isolates), and *P. aeruginosa* (17 isolates). Twenty urine isolates identified multiple organisms consisting of a combination of *E. coli* and *K. pneumoniae* (10 isolates), *Acinetobacter baumannii* and *E. coli* (2 isoates), and *P. aeruginosa* and *K. pneumoniae* (8 isolates). All culture reports showed > 10^5 CFU/ml. The organisms isolated are represented as percentage of total isolates in Figure 2.
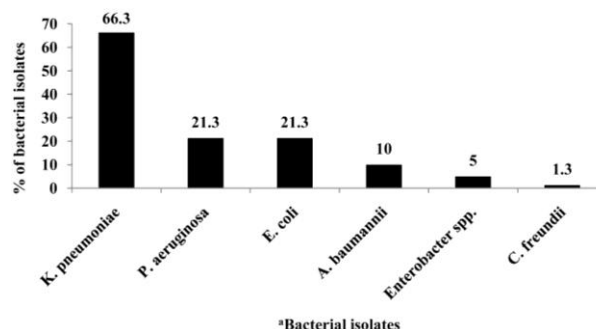
Fig. 2: Various gram negative bacteria isolated from urine specimens (n=100) [a]Two bacteria were isolated from the urine specimens of 20 patients.

Nephrotoxicity was the only ADR observed in UTI patients treated with colistin. Nephrotoxicity as defined earlier (DeRyke *et al.,* 2010) was manifested in 29/80 (36.3%) patients. The mean time for onset of elevation in serum creatinine was 5.48 ± 3.41 days (mean 5 days, median 1-18 days). As per Naranjo ADR probability scale (Naranjo *et al.*, 1981), 18/29 (62.0 %) of the ADRs were 'Probable' and 11/29 (37.9 %) 'Possible'. As per RIFLE (Kellum *et al.,* 2008) criteria, 13/80 (16.3%) patients developed nephrotoxicity i.e. 7/80 (8.8%) patients were categorized as 'risk' and 5/80 (6.3 %) categorized as 'injury' and one patient (1.3%) as 'loss'. Fifty one (63.7 %) UTI patients treated with colistin did not experience any nephrotoxicity. The serum creatinine of 18/29 (62.0%) patients normalized up on discontinuation of colistin. None of the patients received concomitant nephrotoxic medications or radio contrast media

during colistin therapy. No neurotoxic adverse effects were observed in the colistin treated patients. Sixty four (80%) patients treated with colistin had a favourable outcome while 16 (20%) showed unfavourable clinical outcome. Out of the 16 patients with unfavourable outcome, 9 died during colistin therapy, 4 had incomplete therapy due to socioeconomic issues (unable to afford total cost of colistin therapy), and 3 patients did not have evidence of microbiological eradication.
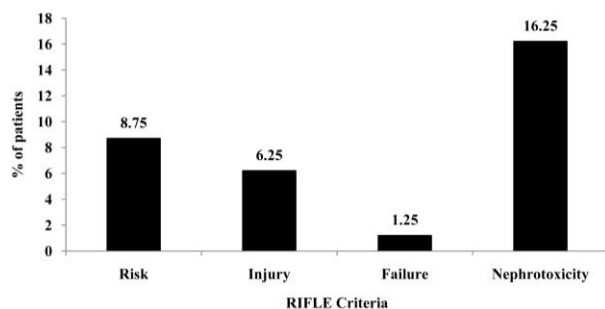
Fig. 3: UTI patients treated with colistin experiencing nephrotoxicity as per RIFLE criteria

Majority of our patients treated with colistin for UTI had a favourable outcome though they were infected with MDR pathogens which were susceptible to colistin. But nearly one third of the patients suffered renal toxicity due to the drug. Many of the patients recovered from renal dysfunction on discontinuation of colistin. None of the patients received concomitant nephrotoxic medications. No other adverse effects including neurotoxicity were observed in these patients. The incidence of renal toxicity in our study was found to be 36.3% (29/80). But reported value (Spapen H *et al*., 2011) in the literature goes up to 53.5 %. Colistin can cause acute tubular necrosis manifested as a rise in serum creatinine and a decrease in creatinine clearance. Nephrotoxicity is dependent on dose and duration of colistin therapy, co-administration of other nephrotoxic drugs, and patient-related factors such as age, sex, hypoalbuminemia, hyperbilirubinemia, underlying disease and severity of the patients' illness (Javan *et al*., 2015). The mean length of drug exposure in our study was 11.41 ± 1.4 days. The median dose of colistin in our study was 2 MU (range 1-9 MU). More than half of the patients (44/80, 55%) diagnosed with UTI in our study were elderly (> 60 years). The maintenance dose of colistin was given based on calculated creatinine clearance of respective patients. A retrospective cohort study (Pogue *et al.*, 2011) from Detroit medical centre on 126 patients treated with colistin in the same dose range as in our study but with majority in the 3-6 MU range found 43% incidence of nephrotoxicity when evaluated by RIFLE criteria. The incidence of nephrotoxicity in our study was found to be 16.75% as per RIFLE criteria. Measures such as adequate hydration, avoidance of concurrent nephrotoxic drugs and regular monitoring of renal function with appropriate dose adjustments may minimize nephrotoxicity of colistin.

Though colistin can cause neurotoxicity (Javan *et al*., 2015) such as facial paresthesia, ophthalmoplegia, difficulty in swallowing, ataxia, eyelid ptosis, partial deafness, visual disturbances, vertigo, confusion, hallucinations, seizures, ataxia and rarely neuromuscular blockade leading to respiratory failure, none of our patients developed any neurotoxic manifestations. Neurotoxicity was absent in other reports (Javan *et al*., 2015, Koomanachai *et al*., 2007, Levin *et al*., 1999, Falagas *et al*., 2015) of colistin therapy as well. The prevalence of neurotoxicity with colistin is considerably less as compared to its nephrotoxicity (Javan *et al*., 2015). Colistin was empirically administered only to 11 critically ill UTI patients, who were referred from other hospitals as part of salvage therapy. Effectiveness of colistin in UTI was assessed based on factors such as resolution of signs and symptoms of UTI, decreasing trend of elevated lab parameters towards normal levels (temperature, WBC, CRP) along with evidence of microbiological eradication of the causative bacteria as per C/s reports showing no growth after 48 hours of discontinuation of colistin. Though only a small fraction of CMS is converted to active colistin in the blood, the unconverted CMS is excreted into the urine by tubular secretion and hydrolyzed in the aqueous system leading to high urinary concentrations of colistin (Bergen *et al*., 2006, Bergen *et al*., 2012). Hence CMS has a potential advantage in the treatment of UTI. This may be the reason for attainment of 80% cure rate of UTI in our study. This is in spite of the fact that only 10 patients in our study received a loading dose of colistin. Loading dose was suggested (Falagas *et al.,* 2005) to attain rapidly a drug concentration equivalent to steady state plasma concentration. Physicians were nevertheless reluctant to practice this due to the fear of development of nephrotoxicity. Colistin combination therapy for MDR gram negative pneumonia was found to improve significantly the microbiological cure without improvement of clinical cure (Parchem *et al*., 2016). Among various drugs tested for in vitro synergy, rifampicin (Etrosillo *et al*., 2008) showed the maximum effect with almost 100% synergy for *A. baumannii*. In our study, for 69/80 (86.25%) UTI cases, the isolated organisms were resistant to all antibiotics including meropenem. But due to the hospital policy of combination therapy, colistin was used in combination with meropenem or other broad spectrum antibiotics in our patients. Combinations of colistin with tigecyclin, minocyclin, meropenem and imipenem have been reported to be synergistic depending on the bacterial isolate tested (Giamarellos-Bourboulis *et al*., 2001, Liang *et al*., 2011, Souli *et al*., 2009, Tumbarello *et al*., 2012).

The cationic polypeptide ring of the colistin molecule binds to the anionic phosphate moieties in the cell membrane of the gram negative bacteria (GNB) causing displacement of calcium and magnesium ions needed for cell membrane integrity. As a result, permeability of the cell membrane increases causing leakage of cell contents and eventually cell death. The disruption of the cell membrane integrity renders the GNB susceptible to previously resistant antibiotics such as crabapenems, tetracyclines and even glycopeptides (Balaji *et al*., 2011). Combination therapy will not only provide a synergistic effect but also prevent development of heteroresistance to polymixins (Zusman *et al*., 2013). In order for the active free base to be released, the sodium

salt must be hydrolysed at body temperature at physiological pH in aqueous systems (Bergen *et al.*, 2006). It was suggested that sufficient conversion of colistin to active metabolite takes place in the bladder resulting in high urinary concentration (Bergen *et al.*, 2006). Since high urinary concentrations of colistin are expected with parenteral administration of CMS, effectiveness of colistin monotherapy or use of colistin without a loading dose for treatment of UTI and also the influence of such a practice of monotherapy on cost effectiveness and development of resistance towards colistin needs to be explored.

CONCLUSION

Our study has confirmed the effectiveness of colistin methane sulphonate for treatment of UTI due to MDR pathogens susceptible to colistin when administered parenterally. But utilization of colistin should be done cautiously with close monitoring of serum creatinine and only for those selected patients with MDR gram negative bacterial infections due to its infamous nephrotoxic adverse effects.

Conflicts of interest: There are no conflicts of interest.

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