Original article

Inhaled colistin for the treatment of nosocomial pneumonia due to multidrug-resistant Gram-negative bacteria: A real-life experience in tertiary care hospitals in Saudi Arabia

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ARTICLE INFO

ABSTRACT

Background: Nosocomial pneumonia (NP) due to multidrug-resistant (MDR) Gram-negative pathogens, has continued to rise over the last several decades. Parenteral administration of colistin results in poor alveolar penetration and subtherapeutic concentration; therefore, direct drug deposition at site of infection may improve the effectiveness while minimizing the systemic exposure. The aim of this study is to describe the safety and effectiveness of inhaled colistin for the treatment of NP caused by MDR Gram-negative pathogens.
Method: Patients who received inhaled colistin from May 2015 to May 2019 at 2 different tertiary care hospitals in Riyadh, Saudi Arabia were identified from pharmacy databases and their charts were retrospectively reviewed.
Results: 86 patients were enrolled in this study. The mean age was 56 ± 20 years. The mean Acute Physiology and Chronic Health Evaluation (APACHE II) was 17 ± 5. The responsible pathogens for NP were Pseudomonas aeruginosa (60%) Acinetobacter baumannii (28%), and Klebsiella pneumoniae (9%). Most patients (76/86) received concomitant intravenous antibiotics. Mean colistin total daily dose was 6 ± 3 million international units divided into 2–3 doses. Mean inhaled colistin duration of therapy was 11 ± 6 days. Favorable clinical outcome was achieved in 51 (59%) patients while favorable microbiological outcome occurred in 29 (34%) patients. Death due to all causes was noted in 39 (45%) cases. Renal injury occurred in 19 (22%) patients, all received concomitant intravenous colistin.
Conclusion: Inhaled colistin can be considered as salvage therapy as adjunct to intravenous administration for treatment of patients with NP due to MDR Gram-negative pathogens.

1. Introduction

Nosocomial pneumonia (NP) due to multidrug-resistant (MDR) Gram-negative pathogens, predominantly Pseudomonas aeruginosa, Acinetobacter baumannii, and Klebsiella pneumoniae has continued to rise over the last several decades and accounts for a substantial clinical and economic burden on healthcare systems (Falagas and Kasiakou, 2005; Gurjar, 2015; Kalil et al., 2016) The limited available treatment options and the lack of novel antibiotics in the pipeline further complicates the situation. These challenges have led to the resurrection of colistin as salvage therapy, the antibiotic that was widely used between the 1960s and 1980s and still active

against these organisms (Falagas and Kasiakou, 2005; Gurjar, 2015; Kalil et al., 2016).

Using intravenous colistin to treat pneumonia is challenging especially when targeting organisms with increased minimum inhibitory concentrations (MICs) because parenteral administration results in poor alveolar penetration (Boisson et al., 2014; Lu et al., 2010). Inhaled route provides direct drug deposition to the site of infection while minimizing systemic exposure (Boisson et al., 2017; Boisson et al., 2014; Lu et al., 2010). This, theoretically, increases antimicrobial efficacy, minimizes antimicrobial resistance, and allows using a dose-sparing strategy to reduce colistin induced nephrotoxicity and neurotoxicity.

Most of the data about the real-life experience on the use of inhaled colistin came from studies on patients with cystic fibrosis (CF). There is relatively limited experience on the use of inhaled colistin in the treatment of NP due to MDR Gram-negative organisms and there is still no consensus on the optimal dosing, dosing interval, duration of therapy, and patient population most likely to benefit. In addition, no study has yet been published in Saudi Arabia describing the safety and effectiveness of inhaled colistin in the treatment of NP. Therefore, the objectives of this study are to describe the use of inhaled colistin for the treatment of NP caused by MDR Gram-negative pathogens in patients without CF and to evaluate the safety and effectiveness of inhaled colistin as monotherapy or as adjuncts to intravenous antimicrobials.

2. Method

2.1. Study design

Patients who received inhaled colistin from May 2015 to May 2019 at King Saud University Medical City and King Fahad Medical City, Riyadh, Saudi Arabia were identified from pharmacy databases and their charts were retrospectively reviewed. Patients 18 years or older who were diagnosed with NP including ventilator-associated pneumonia (VAP) due to MDR Gram-negative pathogens who received inhaled colistin from May 2015 to May 2019 for at least 48 h as monotherapy or adjunct to intravenous antibiotics were included. Patients < 18 years of age including neonates and children, patients with CF, and patients who received inhaled colistin for < 48 h were excluded. Colistin doses were reconstituted in 4 ml sterile normal saline for injection and administered via vibrating mesh or jet nebulizers. The positioning of the vibrating mesh nebulizer is on the inspiratory limb 15 cm from the Y-piece. Filter of the heat and moisture exchanger was removed from the circuit during aerosolization and replaced thereafter. One million international unit (MIU) of colistin is equivalent to ~30 mg of colistin base activity and ~80 mg of the prodrug colistimethate sodium (CMS). The Institutional Review Board in both hospitals approved the study.

2.2. Study variables

Data collection sheet was created to collect specific information including: demographics (medical record number, age, and gender), reason for admission, patient location, Acute Physiology and Chronic Health Evaluation (APACHE II) score, duration of hospitalization, method of specimen sampling and culture, co-morbidities, concomitant antibiotics, duration, dose, and frequency of inhaled colistin and concomitant intravenous colistin. Culture data before and during treatment, laboratory findings before and after treatment including white blood cells (WBC), serum creatinine, procalcitonin (PCT), C-reactive protein (CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) were also collected. Clinical efficacy outcome (cure, improvement or failure including mor-

tality) microbiologic outcome (eradication, persistence or indeterminate), safety outcomes (nephrotoxicity, neurotoxicity, and bronchospasm) were evaluated. Data extraction was performed and study outcomes were assessed by one author and independently confirmed by a second author.

2.3. Microbiological testing

Identification and susceptibility tests of *P. aeruginosa*, *A. baumannii*, and *K. pneumoniae* were performed using commercial broth microdilution method [ComASP Colistin (Liofilchem, Roseto degli Abruzzi, Italy)]. Tested antibiotics include aminoglycosides, carbapenems, cephalosporins, colistin, fluroquinolones, piperacillin/tazobactam, and tigecycline. Susceptibility to colistin was also tested using the E test methodology. The breakpoints and susceptibility interpretive criteria were those defined by the Clinical and Laboratory Standards Institute (CLSI). Bacterial isolate was interpreted as susceptible to colistin if MIC was ≤ 2 mcg/ml.

2.4. Definitions

Pneumonia is defined as new lung infiltrate plus clinical evidence suggestive of pulmonary infection including a new onset of fever, purulent sputum, leukocytosis, and decline in oxygenation. NP is pneumonia occurring at least 48 h after hospital admission while VAP is pneumonia occurring at least 48 h after endotracheal intubation (Kalil et al., 2016). MDR organism was defined as non-susceptibility to at least one agent in three or more antimicrobial categories while colistin-only susceptible when the isolate was resistant to all possible antimicrobial agents except colistin. APACHE II is a commonly used scoring system in critically ill patients to assess disease severity and predict clinical outcome, typically mortality.

Clinical cure is defined as a complete resolution; clinical improvement is defined as partial resolution while clinical failure is defined as persistence or worsening of signs and symptoms attributable to the infection by the end of treatment. Clinical outcome also includes radiographic and laboratory outcomes. Definition of positive clinical outcome (cure or improvement) is based on fever defervescence, reduction in suctioning requirements, decrease or resolution of findings on chest X-ray, improvement of arterial blood gas, and normalization of WBC, CRP, and PCT. Pneumonia-related mortality was defined as death that occurred during the course of treatment when the signs of pneumonia persisted.

Microbiologic eradication is defined as the absence of the causative pathogen's growth in the final culture during same hospitalization. Microbiologic persistence is defined as persistent growth of the causative pathogen regardless of clinical outcome. Indeterminate is when no microbiologic evaluation available.

Renal function assessment is based on Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria. Patients will have nephrotoxicity if any of these categories is met during inhaled colistin treatment. Neurotoxicity is defined as any of the following: ataxia, confusion, dizziness, weakness, visual disturbances, or neuromuscular blockade during inhaled colistin treatment.

2.5. Statistical analysis

Descriptive statistics were used to summarize variables. All the variables are presented as number and percentages. Independent *t* test was used to compare continuous variables while the $\chi 2$ test was used to compare categorical variables. A *p* value of <0.05 was considered significant. All statistical analysis was performed using STATA 15.1 (StataCorp LP, College Station, Texas, USA).

3. Results

86 patients fulfilled the criteria for inclusion. The patients were 55 males and 31 females with a mean ± standard deviation (SD) age of 56 ± 20 years. Patients had mean ± SD APACHE II score of 17 ± 5 at day of colistin treatment. The responsible pathogens for NP were *Pseudomonas aeruginosa* (60%) *Acinetobacter baumannii* (28%), and *Klebsiella pneumoniae* (9%). About a quarter of the isolated pathogens were susceptible only to colistin. Most patients (76/86) received concomitant intravenous antibiotics based on susceptibility tests and MICs, usually intravenous colistin or carbapenem. Mean ± SD inhaled CMS total daily dose was 6 ± 3 MIU (range 2–12 MIU) divided into 2–3 doses. Mean ± SD inhaled CMS duration of therapy was 11 ± 6 days. More detailed demographic data and clinical characteristics including comorbidities, clinical setting, reason for admissions, method of specimen sampling and cultures, duration of hospitalization and mechanical ventilation are listed in Table 1.

Hematological and biochemical laboratory values before and after receiving aerosolized colistin therapy are shown in Table 2. Favorable clinical outcome (clinical cure or improvement) was achieved in 51 (59%) patients while favorable microbiological outcome (eradication) occurred in 29 (34%) patients. Death due to all causes was noted in 39 (45%) cases but only 16 (19%) were determined to be pneumonia-related. Renal injury occurred in 19 (22%) patients, all received concomitant intravenous colistin. Table 3 provides more details about the outcomes in patients who received aerosolized colistin therapy. Factors that might influence mortality including age, comorbid conditions, APACHE II score, and inhaled colistin dosing are analyzed in Table 4.

4. Discussion

The main findings of this retrospective study of 86 patients who received inhaled colistin for the treatment of NP due to MDR Gram-negative bacteria include a clinical response rate of 59% and survival rate of 55%. About 46% of the available repeated cultures showed microbiological eradications. Nephrotoxicity was noted in 22% of patients who received inhaled colistin; however, all of them were on concomitant intravenous colistin. One patient developed bronchospasm and no reported neurotoxicity. Our findings are comparable to previously published studies with respect to effectiveness and safety (Hsieh et al., 2016; Lin et al., 2010); however, other studies reported better clinical outcomes.(Charra et al. 2009) Although meta-analyses evaluating the efficacy of inhaled colistin for treatment of NP exist, the included studies vary in terms of study designs, colistin dosing, duration, and concomitant intravenous antibiotics used (Florescu et al., 2012; Gu et al., 2014; Valachis et al., 2015; Vardakas et al., 2018).

The use of inhaled antibiotics continues to be an area of controversy. On the basis of limited lung penetration of intravenous colistin and due to improved clinical cure rate when inhaled antibiotics is added to intravenous route, the Infectious Diseases Society of America (IDSA) recommends the use of inhaled antibiotics including colistin in addition to intravenous route for treatment of pneumonia caused by MDR Gram-negative pathogens (Kalil et al., 2016). In contrast, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommends not to use inhaled antibiotics due to weak evidence of efficacy and the underestimated adverse events (Rello et al., 2017).

The need for inhaled colistin in the treatment of pneumonia is primarily due to inadequate penetration of colistin in the lung parenchyma after intravenous administration. The serum colistin concentrations after the intravenous administration is almost the MIC of Acinetobacter and Pseudomonas (Imberti et al., 2010; Markou

Table 1
Demographic and clinical characteristics of included patients N = 86.

Characteristic	No. of patients
Demographic	
Age in years (mean ± SD)	56 ± 20
Gender (male), n (%)	55 (64)
APACHE II score (mean ± SD)	17 ± 5
Comorbidity, n (%)	
Malignancy	10 (12)
Cardiovascular diseases	12 (14)
Cerebrovascular disease	13 (15)
Peripheral vascular disease	2 (3)
Pulmonary diseases	14 (16)
Hypertension	50 (58)
Diabetes mellitus	44 (51)
Chronic renal failure	18 (21)
Liver failure	2 (3)
Neurology disease	12 (14)
Endocrine disorder	5 (6)
Reason for admission n (%)	
Septic shock	36 (42)
Cerebrovascular disease	15 (17)
Cardiovascular causes	11 (13)
Respiratory distress	7 (8)
Malignancy	5 (6)
Others*	12 (14)
Admission to the ICU, n (%)	78 (91)
Isolated pathogen at diagnosis, n (%)	
Acinetobacter baumannii	24 (28)
Pseudomonas aeruginosa	52 (60)
Klebsiella pneumoniae	8 (9)
Other	2 (3)
Method of specimen sampling, n (%)	
Invasive (BAL, mBAL, PSB)	4 (5)
Non-invasive (ETA, sputum induction, nasotracheal suctioning)	82 (95)
Culture method, n (%)	
Quantitative	4 (5)
Semi-quantitative	82 (95)
Antimicrobial susceptibility, n (%)	
Colistin-only susceptible	21 (24)
Concomitant systemic antibiotic therapy, n (%)	
None	10 (12)
Intravenous CMS	66 (77)
Carbapenem	45 (52)
Piperacillin/tazobactam	15 (17)
Tigecycline	8 (9)
Cephalosporin	5 (6)
Fluoroquinolone	4 (5)
Aminoglycoside	2 (3)
Intravenous CMS total daily dose in MIU, (mean ± SD)	8 ± 2
Inhaled CMS total daily dose in MIU, (mean ± SD)	6 ± 3
Duration of aerosolized CMS therapy in days, (mean ± SD)	11 ± 6
Duration of hospitalization, (mean ± SD)	122 ± 97
Duration of mechanical ventilation (mean ± SD)	31 ± 19

Abbreviation: APACHE II: Acute Physiology and Chronic Health Evaluation; BAL: bronchoalveolar lavage; CMS: colistin methanesulfonate; ETA: endotracheal aspirate; ICU: intensive care unit; MIU: million international unit; mg: milligram; MV: mechanical ventilation; mBAL: mini bronchoalveolar lavage; PSB: protected specimen brush; SD: standard deviation
*Include trauma, neurological diseases, post-surgical complications, and gastrointestinal perforations.

Table 2
Laboratory data for patients who received aerosolized colistin therapy (mean ± SD).

Variable	Before therapy	After therapy
WBC (x 10^9/L)	12 ± 5.5	10.8 ± 5
CRP (mg/dL)	100 ± 77	63 ± 56
Serum creatinine (μmol/L)	139 ± 85	142 ± 90
ALT (IU/L)	35 ± 30	40 ± 33
AST (IU/L)	33 ± 14	35 ± 18

Abbreviation: ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, PCT: procalcitonin; WBC: White blood cells.

Table 3
Outcomes in patients receiving aerosolized colistin therapy N = 86.

Variable	No. of patients (%)
Clinical outcome	
Cure or improvement	51 (59)
Failure	35 (41)
Microbiologic outcome	
Eradication	29 (34)
Persistence	34 (39)
Indeterminate	23 (27)
Overall in-hospital mortality	39 (45)
Pneumonia-related mortality	16 (19)
Nephrotoxicity	19 (22)
Neurotoxicity	None
Bronchospasm	1 (1)

Table 4
Univariate analysis in patients who received aerosolized colistin therapy for nosocomial pneumonia due to multidrug-resistant Gram-negative pathogens (n = 86) [#][*].

Variable	Surviving (n = 47)	Mortality (n = 39)	P value
Patient characteristics			
Age (years)	51 ± 21	62 ± 17	0.010*
Gender			
Male	30 (64)	25 (64)	0.979
Female	17 (36)	14 (36)	
Comorbidity			
Malignancy			
Yes	3 (6)	7 (18)	0.096
No	44 (94)	32 (82)	
Cardiovascular disease			
Yes	4 (9)	8 (21)	0.11
No	43 (91)	31 (79)	
Cerebrovascular disease			
Yes	8 (17)	5 (13)	0.588
No	39 (83)	34 (87)	
Peripheral vascular diseases			
Yes	1 (2)	1 (3)	0.894
No	46 (98)	38 (97)	
Pulmonary disease			
Yes	7 (15)	7 (18)	0.702
No	40 (85)	32 (82)	
Hypertension			
Yes	24 (51)	26 (67)	0.144
No	23 (49)	13 (33)	
Diabetes mellitus			
Yes	20 (43)	24 (62)	0.08
No	27 (57)	15 (38)	
Chronic renal failure			
Yes	6 (13)	12 (33)	0.041*
No	41 (87)	27 (67)	
Liver failure			
Yes	1 (2)	1 (3)	0.894
No	46 (98)	38 (97)	
Neurological disease			
Yes	7 (15)	5 (13)	0.782
No	40 (85)	34 (87)	
Endocrine disease			
Yes	3 (6)	2 (5)	0.804
No	44 (96)	37 (95)	
APACHE II score	15 ± 6	18 ± 4	0.0092*
Inhaled CMS total daily dose in MIU	7 ± 3.6	5.8 ± 3	0.101
Inhaled CMS total daily dose ≥ 6 MIU	32 (68)	26 (67)	0.889

Abbreviation: APACHE II: Acute Physiology and Chronic Health Evaluation; CMS: colistin methanesulfonate; MIU: million international unit.
[*] Significant p-value of ≤ 0.05.
[#] Data represented mean ± standard deviation or n (%).

et al., 2008). This turned to be subtherapeutic at the alveolar site which can lead to poor response and selection of antibiotic-resistant organisms (Imberti et al., 2010). When administered by inhalation, colistin concentration is 100–1000-folds its plasma concentration. This could enable the use of a dose-sparing strategy to improve efficacy while minimizing the toxicity of systemic exposure (Boisson et al., 2017; Boisson et al., 2014). Decreasing episodes of nephrotoxicity is particularly important as majority of patients who require colistin are critically ill in the intensive care unit with multiple risk factors for acute kidney injury (de Mendonca et al., 2000).

The retrospective design and lack of control group are the main limitations of our study. Further, the dose of inhaled colistin was not standardized. Adverse outcomes could have been underestimated due to the retrospective nature of the study and the fact that the adverse events had to be defined in the medical record as attributable to the antibiotic used. However, to our knowledge, this is the largest single-arm study and the first to describe the use, safety and effectiveness of inhaled colistin for the treatment of NP in Saudi Arabia.

Although a firm conclusion cannot be made, data from this study suggest that inhaled colistin can be considered as salvage therapy as adjunct to intravenous administration for the treatment of patients with NP due to MDR Gram-negative pathogens. Despite the encouraging outcomes, there are many unknowns to be addressed in future studies including optimal concomitant antibiotics, dosing regimen, delivery method, and patients most likely to benefit. Well-designed randomized clinical trials assessing the benefit of inhaled colistin for the treatment of NP due to MDR Gram-negative pathogens are needed.

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