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The Potential Role of Aerosolized Colistin in the Ventilator-Associated Pneumonia Management Caused by Multidrug-Resistant Gram-Negative Bacteria: A Randomized Clinical Trial

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ABSTRACT

Background: Infections caused by multidrug-resistant (MDR) pathogen have caused a resurgence of interest in colistin. To date, information about the effectiveness of Aerosolized Colistin (AS) is very limited in the treatment of Ventilator-Associated Pneumonia (VAP). The aim of this study is to evaluate the efficacy and safety of AS in conjunction with intravenous (IV) colistin in patients with VAP, caused by MDR Gram-Negative Bacteria (GNB).

Methods: This parallel randomized clinical trial was conducted on patients with VAP in the Intensive Care Unit (ICU) ward. 27 patients allocated to the intervention or the control group. Patients in the intervention group received IV Colistin based on glomerular filtration rate along with aerosolized Colistin, 2 million units three times a day. In the control group, only IV Colistin was administered. For all patients, Procalcitonin (PCT), sputum culture, and Clinical Pulmonary Infection Score (CPIS) were evaluated and compared as outcome measures at the specified period of time.

Results: Negative sputum culture was achieved in 9 (80%) out of 11 patients in the AS-IV Colistin group after seven days of therapy versus 9 (56.25%) out of 16 in the control group (P= 0.01). PCT and CPIS scores were not significantly different between two groups (P=0.21, P= 0.62). Furthermore, nephrotoxicity and neurotoxicity were not seen.

Conclusion: AS Colistin lead to earlier negative sputum culture without increasing risk of nephrotoxicity and neurotoxicity, and could potentially be a beneficial adjunctive approach in the management of MDR-VAP.

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Introduction

Patients admitted to the Intensive Care Unit (ICU) have a high risk of mortality not only due to their critical illness but also from secondary complications such as nosocomial infection. Among the nosocomial infections, Ventilator-Associated Pneumonia (VAP) is the most common in ICU patients. VAP has been associated with prolonged duration of ICU stay, higher care costs, morbidity, and mortality (1,2).

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Incident of VAP caused by Multidrug-resistant (MDR) gram-negative bacteria (GNB)—such as Acinetobacterbaumannii, Pseudomonas aeruginosa, and Klebsiella pneumonia—is increasing. Colistin (colistimethate sodium) is an important polymyxin, which has favorable activity against MDR-GNB. However, the polycationic/hydrophilic structure limits its penetration in the lung parenchyma, resulting in systemic toxicity when administered through intravenous route. Inhaled antibiotics can lead to a high concentration of drug in lung tissue without increasing systemic toxicity. Aerosolized (AS) colistin may be considered as a suitable adjunctive treatment of critically ill patients with VAP due to MDR pathogens. Limited data are supporting the effectiveness and tolerability of the inhaled colistin therapy in patients with VAP due to MDR pathogens. Therefore, conducting studies to assess this matter has great clinical significance (3-5).

This study aimed to evaluate the efficacy and safety of AS colistin in conjunction with IV colistin in patients with VAP, caused by MDR-GNB.

Methods

This study was a randomized double-blind clinical trial which was conducted on patients with VAP admitted to the ICU of Dr. Masih Daneshvari Hospital, a university-affiliated referral Hospital. This study was approved by the Ethics Committee of the Shahid Beheshti University of Medical Sciences, Tehran, Iran (Ethics code: IR.SBMU.PHNM.1394.312) with registry code of IRCT20151227025726N9 in the Iranian registry of clinical trials (IRCT). An informed written consent was obtained from all the patients before enrollment in the study. The Investigators and outcome assessors were blind to the study groups until the end of the study.

Sample size was calculated based on 80% of power and 95% of confidence level; and significance level (α) was assumed to be 0.05. The highest number was selected for sample size.

Patients above 18 years, who had a positive culture for MDR-GNB, (MDR is defined as non-susceptibility to at least one agent in three or more antimicrobial categories) (6) sensitive to colistin, and diagnosed with VAP were included in the study. Pregnant patients were excluded.

Block randomization method was used in this study. Eight blocks including four patients were generated with online website (www.sealedenvelope.com/simple-randomiser/v1/lists). In each block, two patients were assigned to the intervention group receiving intravenous and nebulized colistin (IV-AS), and two patients were assigned to the control group receiving intravenous colistin (IV). Investigator, outcome assessors, and data analyst were blind to the study groups until the end of the study.

Demographic characteristics and laboratory findings of patients (procalcitonin [PCT], serum creatinine, creatinine clearance, and complete blood count [CBC] test) were recorded. Acute Physiology and Chronic Health Evaluation II score (APACHE II), Clinical Pulmonary Infection Score (CPIS), and sputum culture were recorded at baseline. Sequential Organ Failure Assessment (SOFA) score, duration of mechanical ventilation, duration of ICU stay, time of initiation and discontinuation of antibiotic therapy were also documented during the study period.

Twenty-seven patients with the diagnosis of VAP were allocated into the intervention or the control group VAP was defined as pneumonia that occurred after 48 hours following mechanical ventilation based on the US Centers for Disease Control and Prevention criteria (7). It was confirmed if at least two or more of the following symptoms were found: 1. fever (body temperature > 38.3°C); 2. leukocytosis (25% increase in WBC count or > 10000 cells/microL) or leukopenia (25% decrease in WBC count or < 5000 cells/microL); and 3. purulent tracheal secretion. Additionally, one of the following criteria must have been met: 1. presence of new and persistent infiltrates on the chest radiograph, 2. the same microorganisms isolated from pleural fluid and tracheal secretions, 3. the radiographic cavitation, 4. histological proof of pneumonia, and 5. positive cultures from bronchoalveolar lavage (≥ 1 × 104 colony-forming units/ ml).

Patients in the intervention group received IV colistin (ColistimethateSodium Injection, powder for solution parenteral 1000000 [IU], Forest Laboratories UK) based on Glomerular Filtration Rate (GFR) (Table 1) plus two million units AS colistin, three times per day, by mesh nebulizer (NIVO vibrating Mesh Nebulizer (Aerogen/Philips). Dose adjustments were implemented, as shown in Table 1 (8,9).

Patients in the control group received only IV colistin. Both groups were prescribed IV colistin until complete resolution of the infection based on culture and clinical response; AS colistin was prescribed only for seven days. To prevent bronchospasm caused by nebulized colistin, patients were premedicated with two to four puffs of salbutamol before the administration of nebulized colistin (18). All patients in two groups received meropenem based on GFR besides colistin.

As primary outcomes, Sputum culture reports and CPIS score were assessed before and within day 4 and 7, after the initiation of antibiotics. Furthermore, PCT measurements were requested and recorded before and on the 3rd, 5th, and 7th day of the treatment.

As secondary outcomes, duration of mechanical ventilation, ICU length of stay, adverse effects, and mortality rate were evaluated.

All the adverse effects associated with the use of colistin—including bronchospasm, nephrotoxicity, neurotoxicity, and hypersensitivity reactions (e.g., rash, pruritus, urticaria, and fever)—were also recorded during colistin administration.

Variables were evaluated for the normality of distribution using the Kolmogorov–Smirnov test. Student's t-test compared the distribution of parametric variables between control and treatment groups. For non-parametric variables, the chi-square test and Mann–Whitney signed-rank test were used for dichotomous or continuous variables, respectively. Variables significantly associated with the study's outcomes in the bivariable analyses were entered in a multivariable backward, stepwise, logistic regression model. Variation of serum creatinine and PCT have been evaluated by Repeated Measures ANOVA. ANOVA test was performed to evaluate PCT variation between the control and the intervention groups.

Moreover, Generalized Estimating Equations (GEE) model was used for modifying the correlation of the studied variables. For all the tests, a two-tailed $p \leq 0.05$ was considered to be statistically significant. Statistical analyses were performed using SPSS version 21.

Table 1. Intravenous colistin for the treatment of MDR gram-negative infections, patient category, and dosing suggestions (9).

Dose	Patient category	Dosing suggestion
Loading	Critically ill or severe sepsis	9-12 MU
Maintenance	eGFR > 60 ml/min	4.5 MU twice a day
	eGFR 30-60 ml/min	3 MU twice a day
	eGFR 10-30 ml/min	2 MU twice a day
	eGFR < 10 ml/min	1 MU twice a day
	Intermittent haemodialysis	1 MU twice a day, then 1 MU after every dialysis
	Continuous renal replacement	4.5 MU twice a day

Results

Over study period, thirty-four patients with MDR-gram negative VAP, who were eligible for colistin administration, were identified. Two patients were excluded due to their age and the remainder thirty-two patients were randomly assigned to the control and the intervention groups. Sixteen patients in the control group and 11 patients in the intervention group were finally analyzed (Figure 1).

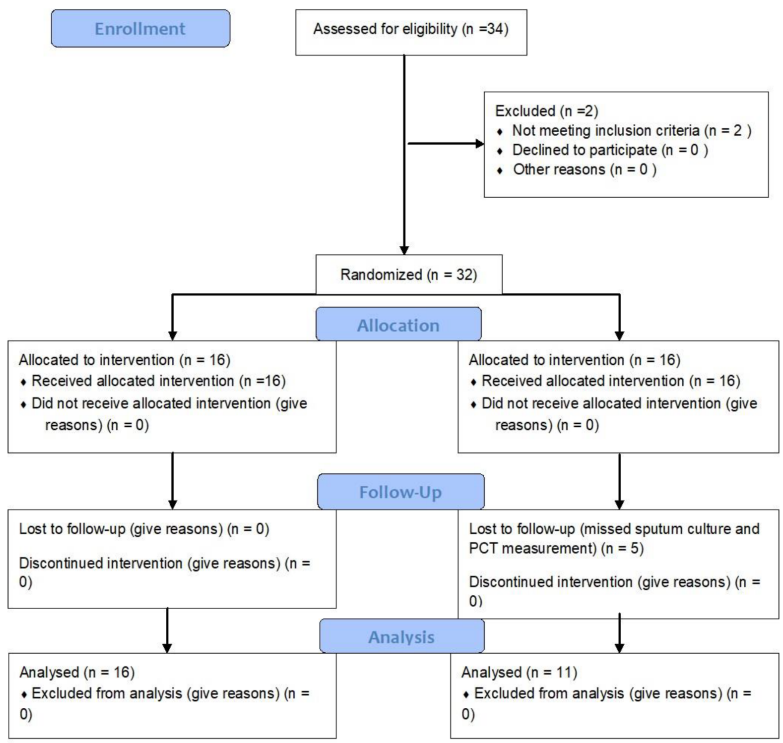

Figure 1. CONSORT Flow Diagram.

No significant differences were found between the control and intervention groups regarding baseline demographic and clinical characteristics, except for Chronic Obstructive Pulmonary Disease (COPD) (Table 2). Patients with COPD were significantly more in the intervention group (P= 0.001).

Table 2. Demographic and clinical characteristics of patients.

Characteristic mean ± SD	AS+IV colistin group (n = 11)	IV colistin group (n = 16)	*p* value
Age	64.64 ± 21.39	66.25 ± 18.59	0.84
Male	7 (39%)	11 (61%)	1.00
Female	4 (44.4%)	5 (55.6%)	1.00
Mean APACHE II score First day of ICU stay	17.73 ± 8.11	16.94 ± 6.48	0.78
Mean SOFA score at baseline	7.19 ± 2.34	6.67 ± 2.28	0.57
CPIS score at baseline	3.82 ± 1.66	3.75 ± 1.24	0.62
Diabetes mellitus	0 (0%)	4 (25%)	0.27
COPD	6 (54.54%)	1 (6.25%)	0.01
HTN	3 (27.27%)	6 (37.5%)	0.69
Opium consumption	2 (18.18%)	2 (12.5%)	1.00
Smoking status	5 (45.45%)	2 (12.5%)	0.08
Causative organisms			
Acinetobacterbaumannii	7 (63.63%)	12 (75%)	0.41
Klebsiella pneumonia	3 (27.27%)	3 (18.75%)	0.66
Pseudomonas aeruginosa	1 (9.09%)	1 (6.25%)	1.00
Duration of ICU stay (days)	26.13 ± 19.69	53.09 ± 49.09	0.11
Duration of MV (days)	23.75 ± 17.47	48.54 ± 43.82	0.11

Data are no. (%) of patients, unless otherwise indicated. AS-IV, Aerosolized plus IV; CPIS, Clinical Pulmonary Infection Score; MV, Mechanical Ventilation; SOFA, Sequential Organ Failure Assessment; VAP, Ventilator-Associated Pneumonia; COPD, Chronic Obstructive Pulmonary Disease;HTN, Hypertension; SD, Standard Deviation; ICU, Intensive Care Unit.

A significant difference was found in sputum culture outcomes between the study groups. Negative sputum culture was achieved in nine (80%) out of the 11 patients in the AS-IV colistin group after seven days of therapy, and in nine (56.25%) out of the16 patients in the IV colistin group (P= 0.01).

Pathogens responsible for VAP were A. baumannii (19 cases [70.37%]), K. pneumonia (6 cases [22.2%]), and P. aeruginosa (2 cases [7.4%]). Two patients in the IV colistin group had concurrent A. baumannii and p. aeruginosa. However, no colistin-resistant strains were isolated from patients in either group.

Evaluation of PCT showed no significant difference between the intervention and the control groups (P= 0.21). There was no significant difference between the CPIS score in the study groups (P= 0.62).

The median length of the ICU stay was the same in both groups (P= 0.11). The median length of the therapy was compared between the study groups: seven days in the AS-IV colistin group and 20 days in the IV colistin group (P= 0.03). There was no significant difference in the duration of mechanical ventilation between the two groups (P= 0.10).

The overall mortality rate in the ICU was 18.1% (2 of 11 patients) in the AS-IV colistin, and 31% (5 of 16 patients) in the IV colistin group (P= 0.66). Kaplan-Meier curves revealed statistically significant differences neither in all-cause mortality (P= 0.66, by log-rank test) nor in VAP-related mortality (P= 0.62, by log-rank test).

Serum creatinine and creatinine clearance were recorded at the beginning of the therapy and daily during seven days of aerosolized colistin treatment. During the study period, 20 patients (74.07%) had an increase in their serum creatinine level less than 0.5mg/dl, of which seven patients (25.92%) had preexisting renal impairment. The serum creatinine returned to baseline within 2-4 days of the therapy. No other adverse events, such as bronchoconstriction, apnea, or chest tightness, were associated with AS colistin therapy. Also, neurotoxicity was not observed in any patient in either group.

Discussion

In the current study, administration of AS colistin as an adjunctive therapy to IV colistin demonstrated more favorable negative sputum

culture, when compared to IV colistin alone (P= 0.01). AS Colistin led to earlier negative sputum culture without increasing risk of nephrotoxicity and neurotoxicity, and could potentially be a beneficial adjunctive approach in the management of MDR-VAP.

The use of aerosolized antibiotics can maximize drug delivery to the lung tissue and also may limit systemic side effects. The advantage of using AS colistin was shown in patients with cystic fibrosis, who were colonized with P. aeruginosa. Inhaled antibiotics were also evaluated in patients with non-cystic fibrosis (CF) bronchiectasis and found to be beneficial. In a study by Lu et al., colistin was not found in the lung tissue after intravenous infusion. However, after nebulization, lung tissue concentration was significantly higher in the lung segments. Local bactericidal activity and low systemic toxicity were also reported in several experimental studies (10-13).

The use of colistin as an adjunctive treatment in VAP patients with MDR-GNB has been evaluated in few studies. These reports disclosed encouraging results, demonstrating a favorable clinical response. Furthermore, microbiological eradication was as high as 18%, and the mortality rates were ranging from 12.5% to 46.7%. However, all these studies had the following limitations: small sample size and absence of a control group (except in the study by Korbila et al.) (11,14).

The focus of some of the studies was on the evaluation of efficacy and safety of AS colistin in conjunction with intravenous colistin, comparing to IV colistin alone. The key results of these studies were in accordance with the beneficial effect of inhaled colistin, without increasing the risk of nephrotoxicity (15-18). In this study, the addition of AS colistin to IV colistin provided an earlier negative sputum culture for patients with MDR VAP caused by gram-negative bacteria. Similar results were reported by Polat et al., (19) in critically ill pediatric patients, which reported a shorter median bacteriological eradication within three days when inhaled colistin was combined with IV colistin. The meta-analysis of Valachis et al., (20) reported a statistically significant improvement in the clinical response and microbiological eradication (OR 1.57; 95 % CI [1.14–2.15]; P= 0.006 and OR 1.61; 95 % CI [1.11–2.35]; P= 0.01, respectively). These findings were not coherent with those of the meta-analysis of Gua et al., (21) that failed to show a difference in the microbiological response (OR 1.29, CI [0.63–2.63], P= 0.48).

Nephrotoxicity and neurotoxicity were reported as the adverse effects of colistin. A systematic review of the toxicity of polymyxin revealed that the incidence of both toxicities was found to be considerably high. However, new pieces of evidence were not in accordance with the previous ones and showed lower toxicity risk with these drugs (22). The nephrotoxicity definition was not standard, which was mentioned as the limitation of the studies (23). Nephrotoxicity of colistin was mainly described with high doses of the drug, when administered intravenously (24).

Nevertheless, the increased risk of renal toxicity was not reported in the studies that used inhaled colistin as adjunctive therapy (16-18). No case of neurotoxicity was reported during the study period. Earlier studies reported paresthesia in about one-fourth of patients receiving colistin, with few cases of neuromuscular blockade or apnea. However, recent studies did not report any significant neurotoxicity (25). Neurotoxicity is also dose-dependent and may be triggered by the presence of risk factors like hypoxia, co-administration of muscle relaxant, narcotics, sedatives, or steroids (24). In the present study, neurotoxicity induced by colistin was not observed.

Inhalation of colistin is generally well tolerated with few reported side effects, including throat irritation, cough, and bronchospasm. The respiratory adverse effects are due to the drug`s osmolality and the presence of preservatives within some of the drug formulations (25). However, in this study, none of the patients in AS and IV groups experienced bronchospasm. Treatment with aerosolized colistin did not affect the weaning of patients from mechanical ventilation. Results were coherent with those of several meta-analyses (20, 21, 26). Nonetheless, Lu et al., reported a prolonged length of ICU stay and a prolonged duration of ventilation in the patients who were in the AS colistin group (27).

The main finding of the present study was that the addition of AS to IV colistin provided earlier negative sputum culture for patients with MDR VAP due to the presence of GNB. In addition, adverse events associated with systemic and AS use of colistin-such as nephrotoxicity, neurotoxicity, and direct toxicity on airways-were not observed.

The main limitation of this study was the small sample size. Another pharmacological limitation was the absence of colistin concentration measurement in lung tissue and plasma.

Our findings revealed that administration of AS colistin caused earlier negative sputum culture. AS colistin did not reduce duration of mechanical ventilation, length of ICU stays, and mortality rate. However, it was found that administration of AS colistin did not increase risk of nephrotoxicity and other adverse effects related to colistin. Further study with more sample size are needed to clarify the potential effects of AS colistin in patients with VAP due to MDR pathogens.

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