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Inhalation plus intravenous colistin versus intravenous colistin alone for treatment of ventilator associated pneumonia

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ABSTRACT

In the setting of intensive care units the incidences of multi-drug resistant gram-negative (MDR-GN) pathogens causing ventilator associated pneumonia (VAP) has increased, leading clinicians to use colistin. Our aim was to assess outcomes associated with the use of inhalation and intravenous colisitn versus only intravenous colistin in patients with MDR-GN VAP. A retrospective, single centre study at University Hospital Centre, Zagreb. Patients were divided in two groups, according to their administration of antibiotics – inhalation and intravenous (INH+IV) administration for 8 patients or intravenous only (IV) administration for 23 patients.

The results showed that demographic and clinical characteristics and the gram negative pathogens isolated were similar between the two groups, except for K. pneumoniae, which was higher in the IV group. No statistically significant difference between the two groups were observed regarding intensive care unit mortality (P=0.951), sepsis (P=0.474), acute respiratory distress syndrome (P=0.548), length of ICU stay (P=0.686) and length of mechanical ventilation (P=0.858). A statistically significant difference was found regarding the eradication of pathogens in respiratory cultures (P= 0.018).

The addition of inhalation to intravenous colistin in MDR-GN VAP improves microbiologic outcome, but does not improve ICU mortality in these patients. Larger prospective trials are warranted to confirm the benefit of adjunctive inhalation colistin as a MDR-GN VAP therapy in the critically ill.

Key words: ventilator-associated pneumoni, Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae

Introduction

Ventilator associated pneumonia (VAP) is a serious and common complication for patients in intensive care units (ICU) and contributes to mortality. (1-4) Gram-negative bacteria, such as Acinetobacter baumanni, Pseudomonas aeruginosa, and Klebsiella pneumoniae, are frequently associated with VAP in the ICU. Unfortunately, the incidence of multi-drug resistant gram-negative (MDR-GN) pathogens is relatively high in the ICU setting. The increased incidence of MDR-GN pathogens and the lack of new effective antimicrobial drugs have lead clinicians to employ colistin again. Colistin was previously removed from use because of nephro- and neurotoxicity. (5,6)

Colistin is a cationic detergent that damages bacterial cytoplasmic membrane, which leads to leakage of intracelular contents causing death. This mechanism of action makes it less susceptible to bacterial resistance mechanisms. (7) There are promising data about the use of inhalation colistin in cystic fibrosis patients. (8,9) Currently,

there are limited and conflicting data on the efficacy and adverse events regarding aerosolized colistin in the treatment of VAP in the critically ill. (10,11,12) The aim of this study is to compare the efficacy and safety of administering inhalation and intravenous colistin versus only intravenous colistin in patients with MDR-GN VAP.

Materials and methods

This retrospective study was conducted at the 13-bed surgical ICU of the University Hospital Centre, Zagreb. Patients ≥ 18 years of age admitted to the ICU between January 2013 and December 2013 were eligible for evaluation of their medical charts. Patients were excluded if they had a diagnosis of cystic fibrosis, had never received appropriate intravenous antibiotics, were mechanically ventilated for < 48 hours, and received ≤ 72 hours of antibiotic therapy. All subjects were enrolled only once. Records of subjects treated with inhalation and intravenous colistin were compared to those who received only intravenous colistin. The following baseline characteristics were collected from the medical records of eligible patients: age, body mass index (BMI), gender, Simplified Acute Physiology Score (SAPS) II, American society of Anesthesiology (ASA) score, comorbid conditions, presence of sepsis, acute respiratory distress syndrome (ARDS) and neutropenia at the time of bronchoalveolar lavage (BAL) or tracheal aspirate (TA). Treatment related factors and clinical outcomes data, including duration of ICU stay, length of mechanical ventilation as well as adverse events to colistin therapy were also assessed. Data were collected from medical records, as well as from pharmacy and microbiology databases. Due to the retrospective nature of the investigation, consent was waived.

Pneumonia was considered ventilator associated pneumonia if the onset occurred after the patient was intubated for ≥ 48 hours and the infection was not incubating before the initiation of mechanical ventilation (6) and when pneumonia was defined on two or more serial chest X-rays or CT-scans with a suggestive image of pneumonia for patients with underlying cardiac or pulmonary disease. In patients without underlying cardiac or pulmonary disease one definitive chest X-ray or CT-scan was sufficient. Additionally, at least one of the following clinical signs or symptoms was required: fever > 38 °C with no other cause, leukopenia (<4,000 WBC/mm3) or leucocytosis (≥ 12,000 WBC/mm3); and at least one of the following (or at least two in cases of clinical pneumonia): new onset of purulent sputum or change in character of sputum, cough or dyspnea or tachypnea, suggestive auscultation, or worsening gas exchange. These factors were considered in combination with a bacteriologic diagnostic performed by: bronchoalveolar lavage (BAL) with a threshold of > 104 Colony Forming Units (CFU)/ml or ≥ 5 % of BAL obtained cells containing intracellular bacteria on a direct microscopic exam (classified on the diagnostic category BAL), protected brush (PB Wimberley) with a threshold of >103 CFU/ml, distal protected aspirate (DPA) with a threshold of > 103 CFU/ml, quantitative culture of Lower Respiratory Tract (LRT) specimen (e.g. endotracheal aspirate) with a threshold of 106 CFU/ml. (13) The primary endpoint of this study was the clinical - ICU mortality. The secondary endpoints were the microbiological outcome - the negativisation of blood and respiratory cultures, and the occurrence of adverse events during colistin treatment. Adverse events during colistin treatment such as nephrotoxicity, neurotoxicity, bronchoconstriction were recorded. Nephrotoxicity was defined as a decline in renal function prompting renal replacement therapy, as a reduction in the calculated creatinine clearance of 50% from the baseline, as failure according to Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE) criteria. (14)

Microbiological testing

Antimicrobial susceptibility testing and interpretation was performed for therapeutically relevant antibiotics on Mueller-Hinton agar using the standard disk diffusion method according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines. (15) Minimum inhibitory concentration (MIC) was determined for all isolates to imipenem, meropenem, and colistin. MICs were interpreted using the criteria established by EUCAST. (15)

Treatment regimen

The daily dose of intravenous colistin was 9 million international units divided into three doses in patients with normal renal function, and a daily dose of additional inhalational colistin was 4 million international units divided into two doses. The nebulizer was positioned in the inspiratory limb of the ventilator circuit. The ventilator system used at the University Hospital Centre during the course of this study was Puritan Bennett. Humidification was discontinued during delivery of the aerosol, and suctioning through the endotracheal tube was avoided following the administration of inhalation.

Statistical analysis

All interval variables followed a normal distribution (according to the Shapiro-Wilkov test) and are presented descriptively as mean values and standard deviations, and differences between groups were tested by the Student's t-test. Variables that use ordinal and nominal scales are shown as the frequency and the differences between groups were tested by the Mann-Whitney U-test (ASA score) or chi-square test. Data analysis was done in STATISTICA version 12 (StatSoft, OK, USA). All p values below 0.05 were considered statistically significant.

Results

During the study period 31 patients were treated with colistin for MDR VAP. Among them 8 patients simultaneously received inhalation and intravenous colisitn (INH+IV), and 23 received intra-

Table 1. Demographics and Clinical Characteristics of Patients treated with inhaled + intravenous colistin and intravenous colistin

		INH+IV	IV	P
Demographics	Age (years)	72.4±11.87	72.5±12.91	0.984*
	BMI (kg/m^2)	24.0±7.59	27.9±7.96	0.230*
	Female sex (N, %)	3 (37.5%)	9 (39.1%)	0.935**
Clinical score	SAPS II score	53.3 ±13.93	49.0±11.62	0.403*
	ASA score(N, %)			
	2	0 (0.0%)	3 (13.0%)	0.268†
	3	3 (37.5%)	12 (52.2%)	
	4	5 (62.5%)	6 (26.1%)	
	5	0 (0.0%)	2 (8.7%)	
Comorbidities (N, %)	Diabetes	1 (12.5%)	8 (34.8%)	0.231**
	COPD	1 (12.5%)	5 (21.8%)	0.568**
	Malignancy	1 (12.5%)	4 (17.4%)	0.746**
	Renal failure	4 (50.0%)	10 (43.5%)	0.749**
Microbiology (N, %)	A. baumanii	5 (62.5%)	12 (52.2%)	0.613**
	P. aeruginosa	7 (87.5%)	19 (82.6%)	0.746**
	K. pneumoniae	0 (0.0%)	5 (21.8%)	0.014**
Colistin without additional antibiotic (N, %)		5 (62.5%)	8 (34.8%)	0.171**
Complications (N, %)	Sepsis	5 (62.5%)	11 (47.8%)	0.474**
	Septic shock	3 (37.5%)	12 (52.2%)	0.474**
	ARDS	0 (0.0%)	1 (4.4%)	0.548**
	Neutropenia	1 (12.5%)	2 (8.7%)	0.754**
	Nephrotoxicity	1 (12.5%)	4 (17.4%)	0.568**
	Neurotoxicity	0 (0.0%)	0 (0.0%)	-
	Bronhoconstriction	1 (12.5%)	0 (0.0%)	0.085**
(days)	Duration of colistin therapy	10.3±5.72	16.9±15.10	0.240*
	Mechanical ventilation	25.1±13.68	23.9±17.91	0.858*
	ICU stay	30.5±11.56	33.8±21.88	0.686*
Clinical outcome(N, %)	ICU mortality	6 (75.0%)	17 (73.9%)	0.951**
Microbiologic outcome(N, %)	Negativisation of respiratory cultures	5 (62.5%)	3 (14.3%)	0.018**

ARDS-acute respiratory distress syndrome; ASA- American Society of Anesthesiology; BMI-body mass index; COPD-chronic obstructive pulmonary disease; ICU-intensive care unit; INH+IV- inhalation + intravenous colistin; IV-intravenous colistin; SAPS II- Simplified Acute Physiology Score

* Student t-test; ** chi-square test; † Mann-Whitney U-test;

venous colistin (IV) alone or in combination with another antimicrobial agent. There were no statistically significant differences in baseline characteristics between the two groups (Table 1). The most common MDR-GN pathogens identified included P.aeruginosa, A.baumanni and there were no differences between the two groups. K.pneumoniae was identified only in the IV group (21.8%, P=0.014). Some patients also had extrapulmonary MDR-GN infections including blood, urine, and soft/skin tissue, and there were no differences between the two groups. Complications including sepsis and ARDS were similar between the two groups. In the INH+IV group one patient (12.5%) was presented with renal dysfunction, while in the IV group four patients (17.4%) were presented with renal dysfunction (P=0.746). Adverse events, such as neurotoxicity, was not recorded, while bronchoconstriciton developed in 1/8 patients in the INH+IV group. The mean duration of colistin therapy was comparable between the two treatment groups: 10.3±5.72 for the INH+IV group and 16.9±15.10 for the IV group (P=0.240). In the two groups the duration of mechanical ventilation (25.1±13.68 vs. 23.9±17.91, P=0.858) and the ICU length of stay (30.5±11.56

vs.33.8±21.88, P=0.686) were not statistically significantly different. The patients receiving colistin INH+IV had better microbiological outcomes - the negativisation of respiratory cultures (5/8, 62.5%) compared to patients in the IV group (3/21, 14.3%, P= 0.018). ICU mortality was similar between the two groups (75% vs 73.9%, P=0.951) (table 1).

Discussion

The present study demonstrated that the addition of INH to IV colistin in patients with MDR-GN VAP did not provide any additional theapeutic benefit it terms of ICU mortality, but provided a benefit in microbiological outcome – that is, the negativisation of respiratory cultures. In addition, adverse events as nephrotoxicity were comparable in both groups. Neurotoxicity was not observed, and bronchoconstriction was only observed in the INH+IV group. Pseudomonas aeruginosa was the most common pathogen, followed by Acinetobacter baumannii and Klebsiella pneumoniae isolated only in the IV group.

In theory, direct delivery of an antibiotic to the site of the infection should be beneficial and might lower systemic adverse effects. In some studies of inhalation colistin added to the IV has shown promising results. (10, 16, 17) However, the results from studies including a control group are not consistent. Korbila et al. demonstrated a better outcome of VAP in patients treated with colistin inhalation than with IV colistin. (12) By contrast, other studies showed no additional benefit. (11,18) The study of Korbila et al. failed to demonstrate mortality differences between the groups. (12) Data from the present study also failed to demonstrate differences in mortality, but showed that adding aerosolized colistin to IV improves microbiological outcome - the negativisation of respiratory cultures. The lack of statistical significance for mortality may be due to several factors, including a relatively small sample size.

With regard to adverse events, the incidences of nephrotoxicity observed, the main limiting factor for colistin use in the past was found to be comparable with recent reports. (10, 19, 20) Furthermore bronchoconstriction was reported in one patient, which is in line with the study by Kwa et al. (21)

There are several important limitations of our study that should be noted. Inhaled colistin was administered via conventional nebulizers, which do not control the particle size, and therefore the question of the actual amount of the drug being delivered to the lungs remains. The study was performed at a single centre and the results may not be generalised to other centers. Furthermore, the retrospective and observational nature of this study limits our ability to establish causality between the use of inhalation antibiotic therapy and ICU survival.

Conclusion

In conclusion, the present study demonstrated a better outcome in negativisation of respiratory cultures when inhaled colistin was used in combination with intravenous colistin (INH+IV) compared to IV colistin alone. Well-designed randomized controlled trials are needed to verify the additional benefits of inhaled colistin in the ICU setting.

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