https://doi.org/ 10.33472/AFJBS.6.10.2024.5213-5221

Efficacy and Safety of Combined Parenteral and Inhaled Colistin Versus Systemic Colistin in Critical Ill Patients with Ventilator Associated Pneumonia

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Article History

Volume 6,Issue 10, 2024

Received:30 Apr 2024

Accepted : 28 May 2024

doi:10.33472/AFJBS.6.10.2024.5213-5221

Abstract

Background: Ventilator-associated pneumonia (VAP) is a type of hospital-acquired pneumonia that develops after more than 48 hours of mechanical ventilation

Aim: To reveal the efficacy of combined parenteral and inhaled Colistin versus systemic Colistin in treatment of critical ill patients with multidrug and extensive drug resistant Ventilator Associated Pneumonia

Patients and methods: This study was conducted on 60 patients meeting the criteria for ventilator associated pneumonia. They divided into group I: consisted of 30 patients subjected to the combined systemic and inhalational Colistin treatment & group II: included the remaining 30 patients subjected to the systemic treatment only. Patients were admitted to International Medical Center and Cairo University Hospitals over a period of two years starting from October 2020 to October 2022.

Results: Overall resolution of VAP was superior in the combined group (12 patients) (40%) in comparison to the IV only group (9 patients) (30%). Concerning in hospital mortality, 12 patients from the combined group (40%), and 16 patients from the IV group (53.3%) died (P value = 0.301). Successful weaning of MV of 18 patients (60%) for the combined group, and was 46.7% (14 patients) for the IV group

Conclusion: Combined inhaled and systemic colistin administration resulted in faster weaning of MV and resolution of pneumonia, no significant differences were found regarding mortality or overall length of ICU stay. Inhaled colistin provides direct drug depositions to the infection site, reducing systemic exposure, increasing antimicrobial efficacy and reduceing nephrotoxicity and neurotoxicity.

Key words: VAP, systemic colistin, inhaled Colistin

Introduction

Ventilator-associated pneumonia (VAP) is a type of hospital-acquired (ie, nosocomial) pneumonia that develops after more than 48 hours of mechanical ventilation. It is a common and serious problem, with an estimated incidence of 10 to 25 percent and an all-cause mortality of 25 to 50 percent. Early diagnosis is important because prompt, appropriate treatment can be lifesaving **(1)**.

Infections caused by multidrug-resistant pathogens are associated with increased mortality, length of hospital stay, and hospital costs **(2)**. Patients with infections due to multidrug-resistant organisms usually are chronically or acutely ill and at risk of dying from underlying serious and complex medical illnesses **(3)**.

Colistin (also called polymyxin E) belongs to the polymyxin group of antibiotics. Colistin is bactericidal drug that disrupts the outer cell membrane of gramnegative rods and is primarily used for infections with multidrug-resistant Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter baumannii **(4)**. Acquired resistance to polymyxins is uncommon but increasing worldwide. Additionally, certain gram-negative rods are intrinsically resistant. These include Burkholderia cepacia, Serratia marcescens, Moraxella catarrhalis, Proteus spp, Providenciaspp, and Morganella morganii **(5)**.

Inhaled colistin may be a useful adjunctive therapy in select multidrug-resistant cases but not suggested for routine use in gram-negative pneumonia. If used, inhaled colistin should be administered with caution and must be mixed immediately prior to administration **(6)**.

Penetration of polymyxins into the cerebrospinal fluid is low when administered intravenously. Intrathecal/intraventricular administration of polymyxins has been employed for central nervous system infection due to multidrug-resistant gram-negative organisms **(7)**.

The incidence of renal toxicity ranges from approximately 20 to 60 percent, and renal impairment appears to be reversible. Polymyxin B is associated with a lower risk of nephrotoxicity than colistin. Neurologic toxicity, mainly paresthesias, is also associated with colistin compared to limited data on the risk of neurotoxicity with polymyxin B **(8)**.

The aim of this work was to reveal the efficacy of combined parenteral and inhaled Colistin versus systemic Colistin in treatment of critical ill patients with multidrug and extensive drug resistant ventilator associated pneumonia regarding resolution of pneumonia, weaning of mechanical ventilation, overall length of stay and mortality; and comparing the safety of both regimens regarding development of acute kidney injury.

Patients and methods

This study was conducted on 60 patients meeting the criteria for ventilator associated pneumonia. They were randomly chosen then divided into group I that consisted of 30 patients subjected to the combined systemic and inhalational Colistin treatment & group II included the remaining 30 patients subjected to the systemic treatment only. Patients were admitted to International Medical Center and Cairo University Hospitals over a period of two years starting from October 2020 to October 2022. We initially enrolled 74 patients with ventilator associated pneumonia, subsequently 14 patients were excluded as they were transferred to other hospitals. The remaining 60 patients represented in our study.

Inclusion criteria: Patients with criteria of ventilator associated pneumonia caused by multidrug or extensive drug resistant pathogens with proved susceptibility to colistin for 10 days' treatment course. Ventilator-associated pneumonia (VAP) is a type of Hospital-acquired (or nosocomial) pneumonia (HAP) that develops more than 48 hours after endotracheal intubation.

Exclusion criteria: Contraindications to colistin (e.g., Hypersensitivity), ongoing and progressive renal impairment and pregnancy.

Ethical approval: The study was approved by the Medical Ethics Committe of faculty of Medicine (Cairo University). Informed consents were taken from relatives of all patients included in our study

Methods:

All patients were subjected to the following: History taking, clinical examination, routine laboratory investigations, hemodynamic assessment scoring system: APACHE II (done on admission) and SOFA scoring systems, Base-line 12-leads ECG, Bed side daily chest x-ray and Echocardiography for assessment of systolic and diastolic functions.

Patients who met the inclusion criteria were randomly divided into two groups: (using computer randomizing model) Group (A) 30 patients: received combined systemic and inhalational colistin and Group (B) 30 patients: received systemic colistin only.

Precautions: Pre nebulization with a bronchodilator within 15 minutes prior to administration

Dosing: IV: 2.5-5 mg/kg/day in 2 to 4 divided doses; maximum: 5 mg/kg/day Inhalation:150 mg every 8 hours

Follow up by: chest x-ray daily: Using murray score, lung was divided into four equal quadrants using vertical and horizontal lines. VAP was given score from one to four according to number of quadrants involved. High resolution indicates at least improvement of half number of quadrants involved at the beginning of the study, while low resolution indicates no improvement or more worsening of chest imaging, total leucocytic count daily, daily kidney function tests, CRP every 48 hours, cultures results, weaning of mechanical ventilation and SOFA score every 48 hours

Primary Outcome Measures: evaluation and comparing both protocols included in the study for critical patients with VAP and their feedback results on resolution of pneumonia, weaning of mechanical ventilation, improvement of inflammatory markers and rate of complications**.**

Secondary Outcome Measures: evaluation and comparing both protocols included in the study for critical patients with VAP and their feedback results on overall mortality and length of ICU stay.

Statistical analysis of the data: Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level. The used tests were: Chi-square test for categorical variables, to compare between different groups. Fisher's Exact or Monte Carlo correction for chi-square when more than 20% of the cells have expected count less than 5. Student t-test for normally distributed quantitative variables, to compare between two studied groups. Mann Whitney test for abnormally distributed quantitative variables, to compare between two studied

Results

Table (1): Comparison between the two studied groups according to demographic data

	IV & inhalational (n = 30)		**IV only (n = 30)**		**Test of Sig.**	**p**
	No.	**%**	**No.**	**%**		
Sex						
Male	21	70.0	21	70.0	χ^2=0.0	1.000
Female	9	30.0	9	30.0		

Age (years)				
Min. – Max.	29.0 – 83.0	16.0 – 84.0		
Mean ± SD.	62.80 ± 11.75	60.0 ± 17.17	t=0.737	.0464
Median (IQR)	65.50 (53.0 – 71.0)	66.0 (55.0 – 71.0)		

There was no statistically significant difference between two groups as regard age and sex. (Table 1)

Table (2): CRP comparison in the study groups.

CRP	**IV & inhalational**	**IV only**	**U**	**p**
Day 1	**(n = 30)**	**(n = 30)**		
Min. – Max.	7.0 – 90.0	7.0 – 90.0		
Mean ± SD.	72.60 ± 26.65	76.26 ± 24.75	442.0	0.895
Median (IQR)	90.0 (49.0 – 90.0)	90.0 (73.0 – 90.0)		
Day 3	**(n = 30)**	**(n = 30)**		
Min. – Max.	23.0 – 90.0	14.0 – 90.0		
Mean ± SD.	77.13 ± 24.20	80.27 ± 19.90	436.50	0.812
Median (IQR)	90.0 (87.0 – 90.0)	90.0 (84.0 – 90.0)		
Day 5	**(n = 30)**	**(n = 29)**		
Min. – Max.	19.0 – 90.0	48.0 – 90.0		
Mean ± SD.	76.13 ± 24.64	81.10 ± 13.80	432.50	0.965
Median (IQR)	90.0 (69.0 – 90.0)	90.0 (68.0 – 90.0)		
Day 7	**(n = 29)**	**(n = 25)**		
Min. – Max.	19.0 – 90.0	39.0 – 90.0		
Mean ± SD.	69.76 ± 25.43	78.04 ± 16.67	299.50	0.234
Median (IQR)	89.0 (49.0 – 90.0)	90.0 (64.0 – 90.0)		
Day 9	**(n = 25)**	**(n = 14)**		
Min. – Max.	15.0 – 90.0	32.0 – 90.0		
Mean ± SD.	69.16 ± 26.04	78.14 ± 17.85	152.0	0.515
Median (IQR)	90.0 (46.0 – 90.0)	90.0 (67.0 – 90.0)		

The mean CRP was 73.1 for combined treatment group and was 78.6 for intravenous group. (**Table 2)**

Table (3): cultures recorded in the study groups.

culture	**IV & inhalational (n= 30)**		**IV only (n= 30)**		χ^2	**p**
	No.	**%**	**No.**	**%**		
0	12	40.0	13	43.3	0.332	1.000
1	15	50.0	15	50.0		
2	3	10.0	2	6.7		

Blood and sputum cultures were recorded for Acinetobacter (0), klebsiella (1) and pseudomonas (2) organisms (**Table 3).**

Table (4): Comparison between the two studied groups according to complications

Complications	**IV & inhalational (n= 30)**		**IV only (n= 30)**		χ^2	**p**
	No.	**%**	**No.**	**%**		
No	19	63.3	24	80.0	2.052	0.152
Yes	11	36.7	6	20.0		

Eleven 11 patients (36.7%) developed AKI in the combined group, while 6 patients (20%) in the IV group developed AKI (**Table 4)**

Table (5): Comparison between the two studied groups according to weaning of MV

Weaning	**IV & inhalational (n= 30)**		**IV only (n= 30)**		χ^2	**p**
	No.	**%**	**No.**	**%**		
No	12	40.0	16	53.3	1.071	0.301
Yes	18	60.0	14	46.7		

Successful weaning of MV of 18 patients (60%) for the combined group, and was 46.7% (14 patients) for the IV group (Table 5).

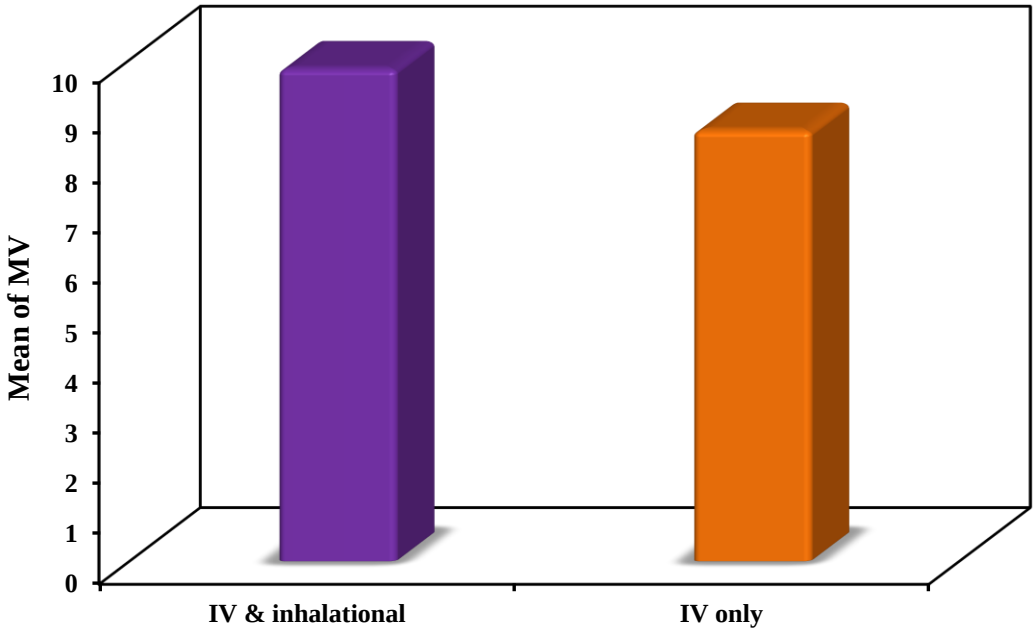

Figure (1): Comparison between the two studied groups according to MV duration
For the combined group, the median was 10 days, and was 8.5 days for the IV group. (Figure 1)

Table 6: Comparison between the two studied groups according to mortality

Mortality	**IV & inhalational (n= 30)**		**IV only (n= 30)**		χ^2	p
	No.	%	No.	%		
No	18	60.0	14	46.7	1.071	0.301
Yes	12	40.0	16	53.3		

Concerning the final outcome of the 60 patients included in our study, 12 patients from the combined group (40%), and 16 patients from the IV group (53.3%) died (**Table 6)**

Table (7): Comparison between the two studied groups according to resolution

Resolution	**IV & inhalational (n= 30)**		**IV only (n= 30)**		χ^2	**p**
	No.	**%**	**No.**	**%**		
Low	18	60.0	21	70.0	0.659	0.417
High	12	40.0	9	30.0		

Overall resolution of VAP was superior in the combined group (12 patients) (40%) in comparison to the IV only group (9 patients) (30%) (**Table 7).**

Discussion

There was no statistically significant difference between two groups as regard age and sex. The mean CRP was 73.1 for combined treatment group and was 78.6 for intravenous group, p value =

0.684) and for cultures results, Blood and sputum cultures were recorded for Acinetobacter (0), klebsiella (1) and pseudomonas (2) organisms

These results agree with **Zampieri FG et al** meta-analysis. Twelve studies were analyzed, including six randomized controlled trials that compared nebulized antibiotics with or without intravenous antibiotics to intravenous antibiotics alone for ventilator-associated pneumonia treatment. The primary outcome was clinical cure. Secondary outcomes were microbiological cure, ICU and hospital mortality, duration of mechanical ventilation, ICU length of stay and adverse events. For the main outcome analysis, 812 patients were included. Nebulized antibiotics were not associated with microbiological cure (RR = 1.24; 95% CI, 0.95 to 1.62; I (2) = 62.5) **(9).**

Successful weaning of MV of 18 patients (60%) for the combined group, and was 46.7% (14 patients) for the IV group while for the duration of mechanical ventilation, for the combined group the median was 10 days, and was 8.5 days for the IV group (P value = 0.066).

Side by side, these results are concordant with **Valachis et al.** meta-analysis that included one randomized trial and seven observational studies comparing aerosolized colistin administered with IV colistin to IV colistin alone in the treatment of VAP, A significant improvement in clinical response (odds ratio, 1.57; 95% CI, 1.14-2.15; p = 0.006; I2 = 37%), microbiological eradication (odds ratio, 1.61; 95% CI, 1.11-2.35; p = 0.01; I2 = 0%), and infection-related mortality (odds ratio, 0.58; 95% CI, 0.34-0.96; p = 0.04; I2 = 46%) was observed with the addition of aerosolized colistin to i.v. treatment, whereas the addition of aerosolized colistin did not affect overall mortality (odds ratio, 0.74; 95% CI, 0.54-1.01; p = 0.06; I2 = 25%) **(10)**.

As regard complications represented by development of acute kidney injury (AKI), in this work 11 patients (36.7%) developed AKI in the combined group, while 6 patients (20%) in the IV group developed AKI (P value = 0.152).

Interrelated findings were reported in **Min KL et al.** retrospective study was performed in a tertiary referral hospital. Data were collected before and after colistin administration between October 2012 and April 2016. A total of 464 patients were enrolled (n = 311, IV group; n = 153, 2nd group). Incidence of AKI was significantly higher in the IV group (IV vs 2nd, 20.26% vs 7.84%, p-value < 0.001). Duration of colistin use (OR 1.033, 95% CI 1.009–1.058, p-value 0.008) and presence of chronic kidney disease (OR 2.710, 95% CI 1.348–5.448, p-value 0.005) were associated with nephrotoxicity. The study concluded that although inhaled colistin alone was not associated with any significant risk factors for nephrotoxicity, duration of colistin use and baseline kidney function may affect aerolised colistin-associated nephrotoxicity which is similar to our study **(11)**.

Against our study, **Kalil AC et al.** meta-analysis that included five randomized trials and four observational studies included as part of the 2016 IDSA/ATS guidelines found that addition of aerosolized colistin to systemic antibiotics in the treatment of VAP had no significant effect on nephrotoxicity (RR, 1.11; 95% CI, .78–1.57). this discrepancy may be explained by underestimation of significant risk factors for nephrotoxicity as duration of colistin treatment and baseline renal functions beside it was performed on populations that had a different profile of risk factors **(12)**.

Overall resolution of VAP was superior in the combined group (12 patients) (40%) in comparison to the IV only group (9 patients) (30%). Concerning in hospital mortality, the final outcome of the 60 patients included in our study, 12 patients from the combined group (40%), and 16 patients from the IV group (53.3%) died (P value = 0.301).

Our results almost interrelate to the former **Kalil AC et al.** meta-analysis that included five randomized trials and four observational studies included as part of the 2016 IDSA/ATS guidelines

with no significant difference between the two groups regarding mortality (RR, 0.84; 95% CI, .63–1.12) **(12)**.

Regarding outcomes & overall ICU stay and mortality, in the same side of our study is prospective study done by **Michalopoulos A, et al** included sixty critically ill patients with a mean APACHE II score 16.7, received aerosolized colistin for the treatment of VAP due to MDR pathogens [Acinetobacter baumannii (37/60 cases), Pseudomonas aeruginosa (12/60 cases) and Klebsiella pneumoniae strains (11/60 cases)]. Half of the isolated pathogens were susceptible only to colistin. Mean (+/-SD) daily dosage of aerosolized colistin was 2.2 (+/-0.7) million international units (IU). All patients received 2946 inhalations of colistin and the mean duration of administration was 16.4 days. Fifty-seven patients received concomitant intravenous treatment with colistin or other antimicrobial agents. Bacteriological and clinical response of VAP was observed in 50/60 (83.3%) patients. All cause hospital mortality was 25% while mortality attributable to VAP was 16.7% **(6).**

Conclusion

Combined inhaled and systemic colistin administration resulted in faster weaning of MV and resolution of pneumonia, no significant differences were found regarding mortality or overall length of ICU stay. Inhaled colistin provides direct drug depositions to the infection site, reducing systemic exposure, increasing antimicrobial efficacy and reduceing nephrotoxicity and neurotoxicity. When administered by inhalation, colistin concentration is 100–1000-folds its plasma concentration. Inhaled colistin can be used as a salvage therapy alongside intravenous administration for treating VAP patients with MDR Gram-negative pathogens.

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