

Empirical colistin inhalation improves ventilatory parameters and severity scoring in Ventilator-associated pneumonia caused by Gram-negative bacteria Empirical-colistin inhalation in VAP

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ABSTRACT

Ventilator-associated pneumonia (VAP) is accompanied by serious complications. The current study assessed the impact of adjuvant nebulized colistin on the outcomes of VAP patients. The study was a prospectively randomized clinical controlled trial done at the international medical center, Cairo, Egypt on VAP. Patients presenting with infection ≥ 48 h of mechanical ventilation (MV) with age ≥ 18 years were included. Patients were excluded when presenting with documented bronchiectasis, cystic fibrosis, known allergy to polymyxin, or with creatinine clearance less than 30ml/min. Eligible patients were randomly assigned to the Control group (20); received empiric IV antibiotic therapy or the test group (20); received an empiric IV antibiotic therapy with adjunctive nebulized colistin three times daily for 7 days. At baseline, both groups were subjected to full data collection, laboratory investigations (CBC, ABG, renal and liver function tests) severity scores (APACHE, SOFA), and chest X-rays. Vital signs, ventilatory status, PaO₂/FiO₂ (P/F ratio), 30- day mortality, weaning off MV, and occurrence of complications were all assessed through the study. Groups were comparable at baseline. APACHE and SOFA scores, WBC count, P/F ratio, mode of MV, and the fraction of inspired O₂ (FiO₂) all significantly improved ($p < 0.005$) in the test versus control groups. The test group improved in weaning off MV, percentage of a negative culture, and the number of deaths ($p < 0.05$) versus control. Adjunctive nebulized colistin improved the severity scores, APACHE and SOFA, ventilatory parameters, and oxygenation with better weaning off MV. It resulted in improved bacteria eradication, chest X-ray finding, and ICU death when compared with conventional therapy.

Keywords: Colistin; Ventilator-associated pneumonia; Nebulization; APACHE; SOFA; Weaning; Mechanical ventilation.

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1. Introduction

Ventilator-associated pneumonia (VAP) occurs after 48-72 h of intubation and mechanical ventilation (MV). VAP develops due to the invasion of lung parenchyma of the lower

respiratory tract by microorganisms. The integrity of the oropharynx and trachea are greatly compromised by intubation allowing oral and gastric secretions to entrance into the lower airways [1]. The diagnosis of VAP is attained by the gradual or sudden onset of dyspnea, signs of

infection (fever, tachypnea, purulent secretions, crackles, etc...), and reduced tidal volume together with laboratory and imaging evidence of infection [1].

According to previous definitions from National Healthcare Safety Network (NHSN), VAP rates varied in developing countries ranging from 10-41.7/1000 ventilator days, and are generally higher than NHSN benchmark rates estimated around 12-19 per 1000 ventilator-days in the US [2]. VAP was estimated to prolong mechanical ventilation by 7.6-11.5 days and hospitalization by 11.5-13.1 days versus those without VAP. The extra cost accompanying VAP was estimated to be around \$40,000/per patient [3, 4]. The crude case-fatality rate of VAP was previously estimated to be around 20%-60% in the US versus 16% to 94% in some developing countries like Egypt [5, 6].

Ventilator-associated pneumonia (VAP) can be polymicrobial. Aerobic gram-negative bacilli (eg, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter spp*, *Pseudomonas aeruginosa*, *Acinetobacter spp*) and gram-positive cocci (eg, *Staphylococcus aureus*, including methicillin-resistant *S. aureus* [MRSA], *Streptococcus spp*) are the most prominent of those pathogens [7, 8]. Nosocomial pneumonia caused by viral pathogens or fungal ones is less common, except in those patients who are immunocompromised. Gram-negative bacilli are the most common pathogens isolated (41-92%), versus Gram-positive cocci (6-58%) [5], among which 50% of those gram-negative isolates are highly resistant to various antibiotics [9].

The emerging era of multidrug-resistance (MDR) caused by Gram-negative bacteria accompanying the deficient new antibiotic molecules, has highlighted the importance of polymyxins [10, 11].

Polymyxin is considered the only available

antibiotic with activity against MDR caused by Gram-negative bacteria; of special concern are *Pseudomonas species*, *Acinetobacter*, and *Klebsiella species* [10, 12, 13]. Polymyxins B and E are those available for clinical use [10]. Colistin was historically used as an intramuscular injection for bacterial infections (gram-negative), but aminoglycosides availability decreased its use because of its significant side effects, particularly nephrotoxicity. Afterward, IV colistin was considered for treating all resistant hospital infections, with *Pseudomonas* and *Acinetobacter* spp especially [14, 15].

Polymyxins, bind to lipopolysaccharides (LPS) and the outer phospholipid cell membrane of bacteria (gram-negative) and disrupt the outer cell membranes, and cause leakage of intracellular contents, and ultimate bacterial death [16-18]. Added to their bactericidal effect, polymyxins bind and neutralize LPS and hence reduce the pathophysiologic effects of endotoxin in the circulation [19, 20]. Resistance to Polymyxins is rare.

Colistin can be administered intravenously, intrathecally, or inhalation as Colistimethate Sodium (CMS) which is a prodrug that produces several derivatives, including the active colistin after hydrolysis from intravenous or inhaled administration. More than 95% of the drug is cleared independently of the kidney. The extravascular distribution and penetration into the various tissues are considered very poorly [21, 22]. Other routes of administration like inhaled and intrathecal administration were formulated to overcome this problem. The role of inhaled administration and its role on gram-negative VAP patients' outcomes still require further studies.

2. Aim of the study

This study evaluated the impact of empirical colistin inhalation as an add-on therapy to

empiric antibiotic therapy for VAP patients and its impact on the clinical outcomes and occurrence of adverse effects of those critically ill patients.

3. Patients and methods

3.1. Design and setting

A prospective controlled randomized clinical trial was conducted at the international medical center, Cairo, Egypt on critically ill patients with VAP. VAP was defined as a presenting after 48 hours of endotracheal intubation and evidenced by the presence of new infiltrates on chest X-ray plus two or more of the following; a fever of >38.3 °C, leukopenia $<4 \times 10^9/L$, leukocytosis $>12 \times 10^9/L$, purulent tracheobronchial secretions or new auscultation evidence of infection and/or reduction in gas exchange.

3.2. Patients

All admitted patients with VAP were screened for eligibility. Those patients aged ≥ 18 years and presenting with infection ≥ 48 h of intubation were included. Excluded patients included those patients with; documented bronchiectasis, cystic fibrosis, known allergy to polymyxin, or with creatinine clearance less than 30ml/min. Eligible patients were randomly assigned following a simple randomization procedure with a (1:1) allocation ratio, into one of 2 arms: Group A or Control group (20 patients); Received empiric IV antibiotic therapy according to the IDSA guidelines [1]; Group B or Treatment group (20 patients); Received an empiric IV antibiotic therapy according to the Infectious Disease Society of America (IDSA) guidelines (1) in addition to Colistin as an adjunctive therapy given three times daily in nebulized form for 7 days.

Nebulized colistin was prepared as 2 million IU colistin diluted in 4 ml sterile normal saline 0.9% using a jet nebulizer connected to the inspiratory limb of the circuit 15 cm from the Y-

adapter. The jet nebulizer was operated at 8 L/min to deliver particle size with a diameter of $\leq 1\mu\text{m}$. Reconstitute the contents of the vial with either water for injections or with sodium chloride 9 mg/ml (0.9% solution).

Colistimethate sodium is very soluble in the reconstitution medium. The recommended technique for dissolving the medicinal product is the addition of 4 mL isotonic sodium chloride solution for the vial containing Colomycin 2 million IU by gentle shaking.

Solutions are for single use only and any remaining solution should be discarded [43].

3.3. Baseline assessment

At baseline, both groups were subjected to full data collection including; demographics, social, medical, surgical, and medication-history-taking. Laboratory data included; complete blood count, arterial blood gases, and renal, and liver function tests. Chest X-ray was done at baseline and whenever required for reassessment. Vital signs were reported initially and continuously throughout the patient's stay. The ventilatory status was assessed by reporting the mode of mechanical ventilation as well as the ratio of the partial pressure of oxygen (PaO_2) to the fraction of inspired O_2 (FiO_2) termed the P/F ratio was calculated.

3.4. Microbiologic assessment

Endotracheal tube aspirate samples were withdrawn for microbiological cultures at day 0 (Start of empiric therapy) and the aspirated sample was initially assessed by Gram's Method. Rapid results (within 12 to 24 h) helped to differentiate between Gram-positive and negative bacteria which guided the completion or cessation of empiric colistin nebulized therapy without the risk of causing bacterial resistance.

3.5. Severity of illness-assessment

Acute Physiology and Chronic Health

Evaluation II “APACHE II” and Sequential Organ Failure Assessment “SOFA” were both calculated for both groups on days 0, 7, and 10.

3.6. Outcome assessment

The primary outcome was the severity of illness assessment and the oxygen support parameters (P/F ratio, FiO₂).

Secondary outcomes Both groups were evaluated for; 30- day mortality, successful weaning from ventilator within 10 days, the occurrence of complications from mechanical ventilation (MV) (e.g. acute respiratory distress syndrome ARDS), or other complications such as cardiac arrest within the whole hospital stay, the occurrence of sepsis within 10 days.

3.7. Follow up

Patients in both groups were monitored daily for the following: the occurrence of side effects from medications, ventilatory status (P/F ratio calculation and mode of mechanical ventilation), vital signs, and laboratory assessment.

All these data were documented daily.

3.8. Ethical Considerations

The ethical committee of the Faculty of Pharmacy at Ain Shams University approved the protocol (Master-63). The study was registered at Clinical Trials.gov (ID: NCT03622450).

3.9. Statistical analysis

Statistical analysis was done using IBM SPSS® Statistics version 22 (IBM® Corp., Armonk, NY, USA). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Pearson’s Chi-square test was used to examine the relation between qualitative variables. Quantitative data were tested for normality using the Kolmogorov-Smirnov test and Shapiro-Wilk test. Exploration of data revealed that the collected values were not normally distributed,

and were presented as median with data range. Comparisons between the 2 groups, concerning categorical data, were performed by the chi-square test. Comparisons between the 2 groups, concerning numerical variables, were done by the Mann-Whitney test, within each period. Change over time for each group was tested using the Wilcoxon signed-rank test for change over time test. All tests were two-tailed. A *p*-value < 0.05 was considered significant.

3.10. Sample size estimation

At the time of study-conduction, no studies were available that assessed the empirical use of colistin inhalation as an add-on to empiric systemic antibiotic therapy for VAP patients. Hence the sample size was calculated using the effect size. A high effect size of 0.8 was expected for colistin inhalation plus the empiric systemic antibiotics for VAP compared to the empiric systemic antibiotics alone. For an aimed power of 0.8 and an alpha error of 0.05, a minimum sample size of 26 patients per arm will be required. An increase of 15 % was added to compensate for patients dropping out to be 30 in each group. Sample size was estimated using the **G*Power® software** (Institut für Experimentelle Psychologie, Heinrich Heine Universität, Düsseldorf, Germany) version 3.1.9.2.

4. Results

Patients’ recruitment and allocation to both groups are represented in the consort flow diagram, **Fig. 1**.

4.1. Baseline assessment

At baseline groups were comparable in all of the following; APACHE score, SOFA score, WBC count, P/F ratio, mode of mechanical ventilation, Fraction of inspired O₂, mean arterial blood pressure (MAP), Glasgow coma scale (GCS), platelet count and bilirubin levels. The median serum creatinine was higher in the control versus the test group, **Table 1**.

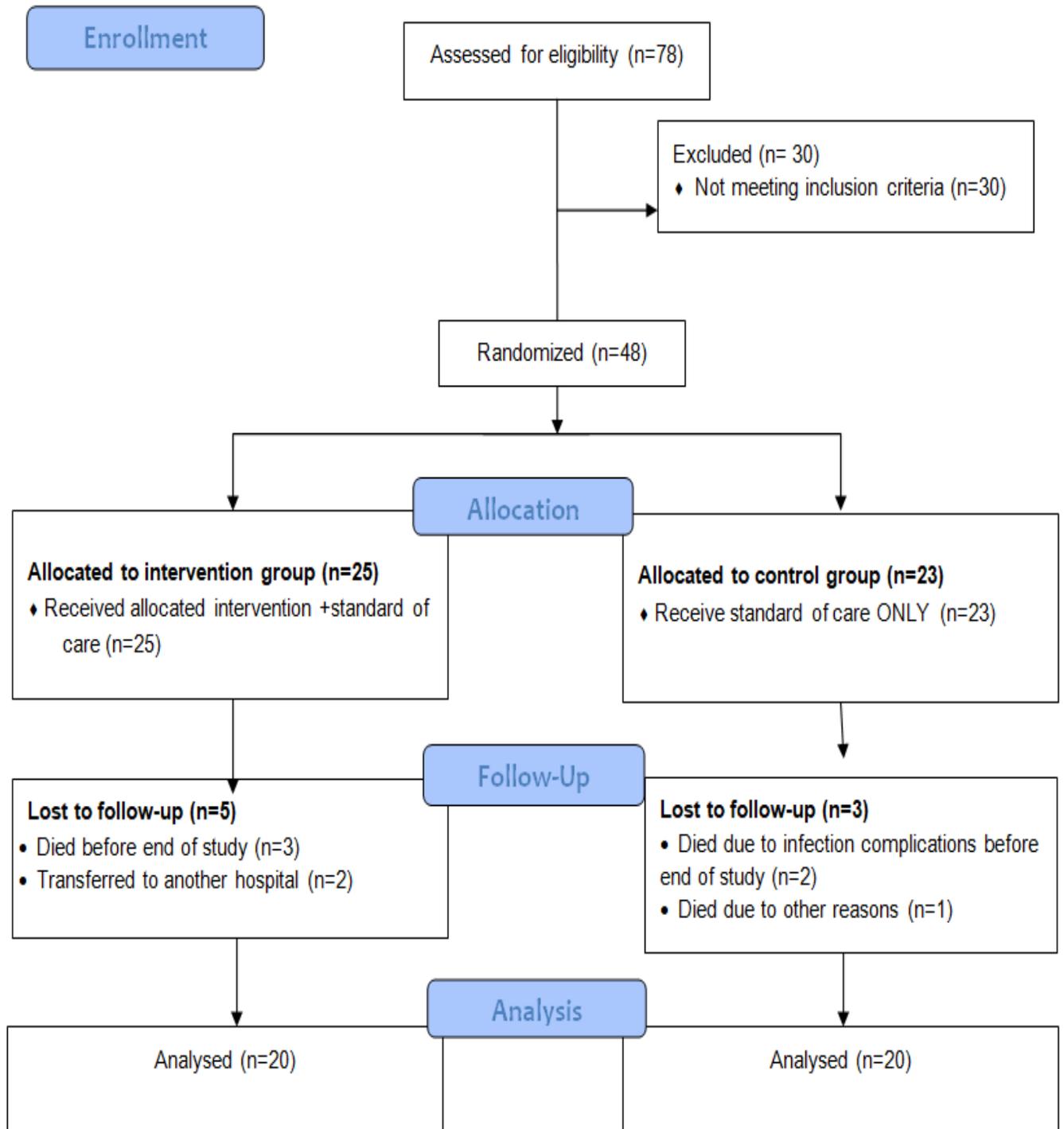


Fig. 1. CONSORT Flow Diagram

Table 1. Baseline comparison between the control and the test groups

	Groups				P-value
	CONTROL (n=20)		TEST (n=20)		
Gender;					# 1.000
Male; n (%)	13 (65%)		13 (65%)		
Female; n (%)	7 (35%)		7 (35%)		
	Mean±S.D	Median (Mini-Max)	Mean±S.D	Median (Mini-Max)	
AGE	50.9 ± 18.3	46.5 (24-80)	46.7± 22.2	44 (17-81)	1.000
APACHE-0		16 (0- 22)		15.5 (5-20)	1.000
SOFA-0		6.5 (3- 8)		5 (3-7)	0.276
WBC-0	13.2± 4	14 (3.9- 20)	15.8±4.1	15.5 (6.5-23.5)	0.432
SCR-0	1.36± 0.38	1.4 (0.41- 1.94)	0.66±0.34	0.57 (0.23-1.36)	*<0.001
PF-0	124.5 ±29.6	125(84.2- 197.5)	130.9±29.3	127 (86.6-185)	1.000
MODE-0		5 (3- 6)		5 (3-7)	0.990
FiO₂ % -0	47.5± 8.4	47.5 (40- 70)	47.5±7.9	50 (40-60)	1.000
MAP-0	91± 13	93.3 (73.3- 113.3)	91.8±8.4	93.3 (73.3- 106.7)	1.000
GCS-0		10.5 (6- 15)		13 (5-15)	1.000
PLT-0	253.6± 63.9	215 (187- 359)	267.7±113.1	247.5 (104- 531)	1.000
BiL -0	0.82± 0.29	0.8 (0.4 - 1.6)	0.88±0.45	0.75 (0.20-1.90)	1.000

Test statistics used was Mann-Whitney; # Chi square test, *p<0.05 was considered significant.

The Control group received empiric IV antibiotic therapy

The test group received empiric IV antibiotic therapy +nebulized colistin adjunctive therapy 3 times daily for 7 days.

0= at baseline; S.D, standard deviation; APACHE, Acute Physiology and chronic health evaluation; SOFA, Sequential Organ Failure Assessment; PF, equals the arterial PO₂ divided by the fraction (percent) of inspired oxygen; FiO₂ %, fraction (percent) of inspired oxygen; MAP, Mean Arterial Pressure; GCS, Glasgow Coma Scale; MODE=mechanical ventilation mode; WBC, white blood cell count; S-Cr, serum creatinine; PLT, Platelets; BiL, Bilirubin.

4.2. Overtime assessment between groups

Clinical scores and laboratory markers were assessed at several time points between the 2 groups; baseline (0) and after 5, 7, and 10 days and other outcome assessments were evaluated till patient discharge or death or until 30 days from inclusion.

4.2.1. Clinical parameters and scores

APACHE score: The comparable APACHE score at baseline was significantly changed over time in both groups (p<0.001). The Control group had a higher median APACHE score from baseline versus day 10 (16 vs 19.5, p= 0.024), while the test group had a lower median APACHE score from baseline versus day 10 (15.5 vs 5.5, p<0.001). The median APACHE score was comparable between the 2 groups at baseline and on day 5, while there was a

significant decline in the median APACHE score in the test group versus control on both day 7 (9 vs 14.5, p=0.03) and day 10 (5.5 vs 19.5, p< 0.001) **Table 2.**

SOFA score: The comparable baseline SOFA score between the 2 groups was significantly changed over time in both groups. The median SOFA score of the control group increased from baseline versus day 10 (6.5 vs 7, p= 0.004), while the test group showed a significant decrease in the median SOFA score from baseline versus day 10 (5 vs 3.5, p<0.009). Comparing the 2 groups, the median SOFA score was comparable between the 2 groups at baseline only, while there was a significant decline in the median SOFA score in the test group versus control at days 5 (4 vs 6, p<0.001), 7 (3 vs 6, p=0.03) and day 10 (3.5 vs 7, p< 0.001) **Table 2.**

Table 2. Overtime assessment between the control and the test groups

	CONTROL		TEST		P-value
	Mean± S.D	Median (Mini-Max)	Mean± S.D	Median (Mini-Max)	
APACHE-0		16 (0- 22)		15.5 (5-20)	1.000
APACHE-5		12.5 (1-20)		10 (0-17)	0.546
APACHE-7		14.5 (2-24)		9 (0-16)	*0.030
APACHE-10		19.5 (0-33)		5.5 (0-15)	*<0.001
P-value		*<0.001		*<0.001	
SOFA-0		6.5 (3- 8)		5 (3-7)	0.276
SOFA-5		6 (4-8)		4 (3-7)	*<0.001
SOFA-7		6 (3-13)		3 (3-8)	*0.030
SOFA-10		7 (3-13)		3.5 (1-8)	*<0.001
P-value		*0.003		*0.034	
PF-0	124.5 ±29.6	125(84.2- 197.5)	130.9±29.3	127 (86.6-185)	1.000
PF-5	108 ±20.3	113 (82.8-140)	180.5±36.5	186.3 (101.4-230.0)	*<0.001
PF-7	102.5 ±16.6	97.3 (71.6-144.4)	191.5±47.7	186.3 (89.2-303.1)	*<0.001
PF-10	85.1 ±32.1	78.5 (45.7-182.5)	227.6±65.3	213.8 (95.3-342.8)	*<0.001
P-value		*<0.001		*<0.001	
MODE-0		5 (3- 6)		5 (3-7)	0.990
MODE-5		5 (3- 6)		5 (1-7)	1.000
MODE-7		5 (3- 6)		5 (1-7)	1.000
MODE-10		5 (3- 7)		3.5 (1-7)	*0.006
P-value		0.300		*<0.001	
FiO2 % -0	47.5± 8.4	47.5 (40- 70)	47.5±7.9	50 (40-60)	1.000
FiO2 % -5	55.0± 7.6	50 (45-70)	44.5± 8.3	40 (35- 70)	*<0.001
FiO2 % -7	58.5± 6.9	60 (45-70)	43.4± 8.3	40 (30- 65)	*<0.001
FiO2 % -10	64.8± 9.1	70 (40-75)	39.1± 8.5	40 (28- 65)	*<0.001
P-value		*<0.001		*0.013	
MAP-0	91± 13	93.3 (73.3- 113.3)	91.8±8.4	93.3 (73.3- 106.7)	1.000
MAP-5	92.2± 10.8	93.3 (73.3-113.3)	92.1± 9.3	93.3 (76.7-110)	1.000
MAP-7	88.4± 11.7	90 (53.3-103.3)	90.7± 7.5	93.3 (73.3-100)	1.000
MAP-10	87.6± 10.2	90 (70-100)	90.6± 7.2	90 (80-113.3)	1.000
P-value		1.000		1.000	
GCS-0		10.5 (6- 15)		13 (5-15)	1.000
GCS-5		11 (5- 15)		15 (6- 15)	1.000
GCS-7		10 (4- 15)		15 (6- 15)	0.648
GCS-10		10 (4- 15)		15 (6- 15)	0.198
P-value		0.081		0.141	

Test statistics; Mann-Whitney for comparison between groups and Wilcoxon signed-rank test for change over time, *p< 0.05 was considered significant.

Abbreviations: -0= at baseline;-5= On Day 5;-7=At Day 7;-10= On Day 10; S.D, standard deviation; APACHE, Acute Physiology and chronic health evaluation; SOFA, Sequential Organ Failure Assessment; PF, equals the arterial pO2 divided the fraction (percent) of inspired oxygen; FiO2 %, fraction (percent) of inspired oxygen; MAP, Mean Arterial Pressure; GCS, Glasgow Coma Scale; MODE=mechanical ventilation mode.

GCS: Both groups were comparable in the GCS at the various time points, 0, 5, 7, or day 10.

MAP: Both groups were comparable in the MAP at the various time points, 0, 5, 7, or day 10.

Mode of ventilation: The mode of ventilation was comparable between 2 groups at baseline. A significant change over time was only observed in the test ($p=0.003$), with an apparent decline in ventilatory support from baseline versus day 10 ($p=0.009$). The control group remained at the same level of ventilatory support over time. A significant decline in the ventilatory support required in the test group versus the control was observed on day 10 (3.5 vs 5, $p<0.006$) **Table 2**.

FiO₂: The baseline fraction of inspired O₂ required for O₂ support was comparable between groups and a change was observed over time in both groups ($p<0.001$). The Control group had an increase in the median FiO₂ required from baseline versus day 10 (47.5% vs 70%, $p<0.001$), while the test group had a decline in the median FiO₂ required from baseline versus day 10 (50% vs 40%, $p=0.013$). A significant decline in the test group median FiO₂ versus control at several time points namely, day 5 (40% vs 50%, $p<0.001$), day 7 (40% vs 60%, $p<0.001$) and day 10 (40% vs 70%, $p<0.001$).

P/F ratio: The P/F ratio was comparable at baseline and significantly changed over time ($p<0.001$). The Control group had a decline in the median P/F ratio from baseline versus day 7 (125 vs 97.3, $p=0.002$) and day 10 (125 vs 78.5, $p<0.001$), while the test group had an improvement in the median P/F ratio from baseline versus day 10 (127 vs 213.8, $p=0.013$). A significant increase in the median P/F in test

versus control at several time points namely, day 5 (186.3 vs 113, $p<0.001$), day 7 (186.3 vs 97.3, $p<0.001$), and day 10 (213.8 vs 78.5, $p<0.001$), **Fig. 2**.

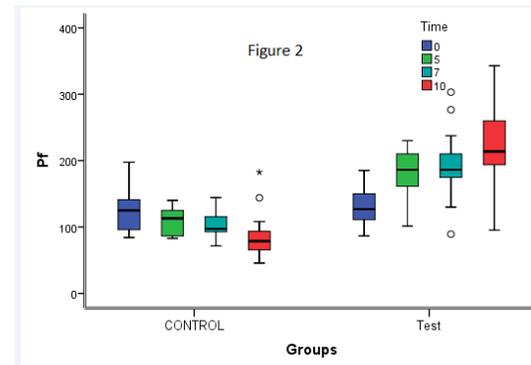


Fig. 2. P/F ratio between the control and the test groups

4.2.2. Laboratory parameters

Serum creatinine: The control group's serum creatinine was significantly higher than the test group at baseline and no change was reported over time between groups. Moreover, a difference was reported on all days, 5, 7, and 10 ($p < 0.001$) between the 2 groups.

WBCs: The WBCs were not different between the 2 groups at baseline and a change was reported over time in both groups ($p<0.001$). The control group had an increase in the median WBC count from baseline versus day 10 (14 vs 17.8, $p=0.004$), while the test group had a decrease in the median WBC count from baseline versus day 10 (15.5 vs 7.7, $p=0.013$). A significant decline in the WBC count in the test versus control was observed at several time points, namely, day 5 (10.1 vs 14.3, $p=0.054$), day 7 (9.4 vs 16.3, $p<0.01$), and day 10 (7.7 vs 17.8, $p<0.001$), **Fig. 3**.

Bilirubin level and platelet count: No difference was reported between the 2 groups in bilirubin level or platelet count at the various time points, 0, 5, 7, or day 10.

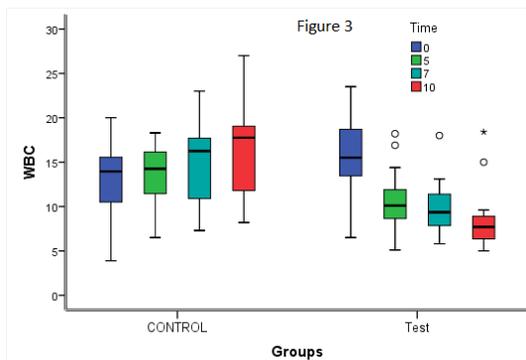


Fig. 3. White blood cell count (WBC) between the control and the test groups

4.3. End of study-assessment between the 2 groups

4.3.1. Weaning off mechanical ventilation

The test group had a significantly higher number of patients who were weaned off mechanical ventilation versus controls (18 vs 2, $p < 0.001$).

4.3.2. Occurrence of complications

The occurrence of *ARDS* or *cardiac arrest* was not different between the 2 groups. While, the test group reported a lesser number of patients who developed *sepsis* versus the control group (1 vs 8, $p = 0.008$).

4.3.3. Chest X-Ray findings

The baseline chest X-ray findings were comparable between groups. No change was observed over time in the control group, while the test group showed an improvement in chest X-ray findings over time ($p < 0.001$). There was a significant clearing in chest X-ray findings in the test versus control after 10 days (1 vs 3, $p < 0.001$).

4.3.4. Culture growth

On day 7, culture results revealed more patients in the test group with no growth versus controls (14 vs 1, $p < 0.001$). On day 10, more patients in the test group had no growth versus controls (18 vs 3, $p < 0.001$).

4.3.4.1. Length of stay was not different between the groups (24 vs 23, $p = 0.925$) respectively.

4.3.4.2. Death. More patients died in the control versus the test group (16 vs 3 $p < 0.001$) respectively.

5. Discussion

Ventilator-associated pneumonia is accompanied by an increased need for mechanical ventilation, a longer ICU stay, and all-cause mortality reaching up to 50% [2].

The current study showed that the use of nebulized colistin as an adjuvant to empiric antibiotics in VAP patients improved clinical outcomes in terms of disease-severity scales, ventilatory parameters, and weaning off mechanical ventilation compared to empiric antibiotics alone.

Various studies have assessed both the efficacy and safety of nebulized colistin as an add-on therapy to IV colistin versus IV colistin alone [23-26] or add on to other antibiotics such as β -lactams [26], doxycycline [27], or tigecycline [28]. While the current study studied the effect of nebulized colistin as adjuvant therapy to empiric antibiotic therapy in patients with VAP versus IV empiric antibiotic therapy. Similarly, another study [41] evaluated targeted objective outcomes of clinical and microbiologic effects after a treatment period of 5 days using add-on nebulized colistin to systemic antibiotics in treating patients with gram-negative VAP.

Since colistin resistance is a matter of concern, the dose regimens used and their adjustment are critical. In the current study, adjunctive colistin therapy was given three times daily in the nebulized form (prepared as 2 million IU colistin diluted in 4 mL sterile normal saline 0.9%) for 7 days, in consistence with other

studies [29], [30] yet lower than those used by Nassar et al [41] study that used an inhaled colistin dose of 3 million units per day.

The underlying indications mandating the need for mechanical ventilation are heterogeneous, which affects the all-cause mortality reported in the various studies. Hence, death may not necessarily be due to VAP alone, but rather due to the complex effects of associated disease severity and multiple organ dysfunction, in addition to the different drug dosages and treatment periods. Hence, baseline severity assessment is mandatory to clarify inter-individual responses between patients and study groups.

The APACHE II score is a severity scoring system whose higher scores correspond to a more severe illness and a higher risk of death. In the current study, the comparable baseline APACHE II score between groups, significantly decreased over time in the nebulized-colistin-group versus the control group, which in turn, significantly increased over time relative to its baseline values. On the contrary, Kim et al. [31] reported an insignificant difference in APACHE scores of adjunctive-nebulized colistin versus IV colistin in VAP caused by *carbapenem-resistant Acinetobacter baumannii* (CRAB). Also, Jang et al, [32] reported no significance when using high doses of nebulized colistin in surgical patients with VAP. The discrepancy between the studies could be attributed to the differences in study criteria, time of score-reporting, and the underlying etiology of ICU admission.

The SOFA score is important in quantifying how severe is a patient's illness by assessing the organ dysfunction degree in six organ failures [33] and is continuously used in the ICU to assess the severity of a patient's illness at weaning or extubation [34]. In the present study, a significant decline was observed in the SOFA score in the nebulized colistin versus the control group on

days 5 and 10.

Moreover, the colistin group had an improvement in the mode of MV use and a decline in the ventilatory support required as well as the FiO₂ in the colistin versus the control group at day 10.

Finally, a significant improvement in oxygenation as expressed by an increase in the P/F ratio was observed in the nebulized-colistin group from baseline versus day 10, contrary to the significant decline in the control group, indicating an improvement in oxygenation that could be attributed to better infection eradication. Following our findings, a randomized, single-blinded study [35], showed an improvement in the P/F ratio with aerosolized (AS) colistin group versus IV colistin on day 14 of therapy with colistin in 149 patients with VAP due to gram-negative bacteria. Moreover, another study [41] that calculated the clinical pulmonary infection score (CPIS) values, concluded that adding inhaled colistin for five days in patients with VAP due to gram-negative bacteria resulted in both a higher clearance and clinical improvement. Similarly, a meta-analysis [36] suggested that colistin in nebulized form may add benefit in the treatment of ICU patients with respiratory infections, and also included studies of patients with tracheobronchitis and non-ventilated ICU-acquired pneumonia. On other hand, a previous meta-analysis [37] showed an insignificant trend for better microbiological response with nebulized colistin compared with the control group. Of course, differences in methodologies, patient characteristics, and outcome reporting can all contribute to the discrepancies between studies.

To wean a patient from mechanical ventilation is to gradually reduce the ventilatory support, reaching a patient who is breathing spontaneously and finally extubated. This is only achieved if the original cause for MV is

improved, while the rest of the cases bear the consequences of prolonged MV with its deleterious effects [43]. In the present study, a higher number of patients have weaned off MV in the colistin adjuvant group versus the control. Similarly, a previous study [25] documented fewer days on MV (8 vs. 12 days, $P=0.001$) in nebulized MDR-VAP. Also, another study [26], using a high colistin dose (15 million/day) showed a decrease in MV days (18 vs. 38 days, $P=0.001$) and decreased hospital length of stay (25 vs. 54 days, $P=0.001$) in the nebulized MDR-VAP group versus the control group, respectively. Moreover, another study [35] reported early weaning from MV in survivors from ICU with a mean gain in ventilator-free days of 5 days.

In the current study, an improvement in chest X-ray findings over time was reported in the colistin-add on group versus controls. On the contrary, in another study [31] radiographic evidence was observed after 3 days in 18 patients in the colistin group and 13 in the control group with no difference. The radiographic clearing up is a favorable outcome of the current study, with the variability in other studies attributable to complex underlying pathologies and causative organisms in each study.

Bacterial eradication was reported in the colistin inhaled group on days 7 and 10 of culture results, indicating a better colistin effect on organism-eradication. These effects elaborate on the current study's positive findings regarding oxygenation and severity scores. Similarly, another study [38] in a pediatric ICU, reported shorter median bacteriological eradication within 3 days when inhaled colistin was combined with IV colistin. A meta-analysis [36] showed significant improvement in clinical response and microbiological eradication. These findings were not coherent with those of an earlier meta-analysis [39] that did not report any difference in

microbiological response. The discrepancy between the meta-analysis and our findings was related to differences in the doses and duration of inhaled colistin therapy and could be considered a favorable outcome even if it was just a presumed eradication without a confirmed follow-up culture result.

In the current study, the ICU length of stay was not different between the groups. Similarly, Kim et al, [31] reported no difference in ICU days of stay after VAP onset between the two groups and no difference in the ICU length of stay and the all-cause mortality at 28 days between both arms [31]. Similarly, Abdellatif et al. showed no difference in survival analysis between groups [35]. Also, these findings were in line with those of other meta-analyses [36], [39]. However, another study [26] reported an increased ICU stay and an increased time of ventilation in the aerosol group.

Regarding the ICU mortality in our study, the inhaled colistin group had a significantly lower number of patients who died than the control. In line with a previous meta-analysis [23], lower mortality was reported in MDR gram-negative hospital-acquired pneumonia when adding aerosolized colistin compared to those receiving parenteral colistin. On the contrary, a previous RCT [30] using colistimethate sodium nebulization added to therapy of patients with Gram-negative-VAP, showed no difference in mortality between the groups. Other studies [31] [35] as well did not report a difference.

Finally, safety is a crucial concern. In the current study, patients tolerated nebulized colistin well, with no reported difference in the occurrence of side effects between groups throughout the whole study duration. In the study group, serum creatinine levels improved from the baseline level, resulting in better outcomes. Similarly, a study [35] that compared inhaled with IV colistin showed lower nephrotoxicity and

requirement for renal replacement in the inhaled group. On the contrary, another study [41] showed no changes in the mean serum creatinine level in either the colistin or control group from day 1 to 5 of therapy.

The majority of the published literature reported that nebulized colistin was generally safe, without significant renal impairment [25, 30, 40]. These findings confirmed the hypothesis of the presence of low systemic diffusion with the use of inhaled colistin.

Conclusion

The use of nebulized colistin as an adjuvant to empirical IV antibiotics improved the severity scores, APACHE and SOFA, ventilatory parameters and oxygenation with better weaning off MV, improved bacteria eradication, chest X-ray finding with a significant decrease in mechanical ventilation-time and ICU death versus regular therapy. Colistin was tolerable with no significant adverse drug reactions.

Limitations

The current study was limited by the small sample size. Patient recruitment was tedious as several patients with VAP were excluded either due to lack of inclusion criteria or due to transfer to another hospital. The long-term follow-up (beyond study duration) of patients was not possible due to the critical illness of this patient population. Financial constraints limited longer evaluation periods and comparison of other colistin doses. Only one dose range was used in the current study.

Declarations

Ethics approval and consent of participation

The study was approved by the ethical committee of the Faculty of Pharmacy Ain Shams University, (Master-63). The study was registered at Clinical Trials.gov (ID:

NCT03622450).

Consent of publication

Not applicable

Data and materials availability

All data produced or analyzed throughout this study are included in the current manuscript.

Competing interests

No competing interests were found between the authors.

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Authors' contributions

The authors of the submitted manuscript are in order; Norhan Abu-Thuraya, Lamia El Wakeel, Mohamed Omar, and Alia Abdelfattah.

All authors contributed to the study's conception and design.

Material preparation, data collection, and analysis were performed by Norhan Abu-Thuraya, Lamia El Wakeel, and Mohamed Omar.

The first draft of the manuscript was written by Norhan Abu-Thuraya, and Lamia El Wakeel **All authors** commented on previous versions of the manuscript.

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