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Assessment of Aerosolized Colistin and Gentamicin in Mechanically Ventilated Patients

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ABSTRACT

Background: Ineffective parental antibiotic use in management of Ventilator associated pneumonia (VAP) open the window for using inhaled antibiotic formula to achieve higher local concentration of antibiotics and subsequently good recovery response. **Objectives:** This work was aimed to evaluate the aerosolized antibiotics (Colistin and Gentamicin) efficacy in improving the mechanically ventilated patient as adjunctive to intravenous systemic antibiotics.

Patients and Methods: This randomized control (RCT) trial study included a total of thirty mechanically ventilated patients, attending at Respiratory Intensive Care Unit (RICU), Chest Diseases Department, Faculty of Medicine, Ain Shams University Hospitals. They were classified equally into three groups; Group I: involved 10 patients who received aerosolized Colistin along with systematic antibiotics (SA), group II: involved 10 patients who received aerosolized Gentamicin along with SA and group III (Control): involved 10 patients who received only SA.

Results: The incidence of VAP was 10%; in group I no cases had VAP, while in group II and controls, just (20 %) and (10 %) of cases had VAP respectively, with insignificant association of VAP with particular group, (P= 0.3). Clinically; only group I showed significant lower degree of temperature in comparison with controls, (P= 0.01). The mean days of MV and ICU in each group were (6.8±2.15; 8.9±3.11, 5.9±2.23; 7.2±2.7, 5.1±1.1; 6.1±1.85) respectively, with insignificant difference between the treatment groups. Finally, the survival rate in group I was 90 %, and was slightly lower in group II and control group; 60 % and 50 % respectively, with insignificant association of survival status in particular group.

Conclusion: It could be concluded that the empirical treatment by aerosolized Colistin was more effective as an adjunctive therapy to SA for VAP protection than aerosolized Gentamicin, it had rapid resolution of respiratory infection signs, and subsequently the MV days, ICU stays and cost but had no effect on mortality.

Keywords: Ventilator associated pneumonia (VAP), Aerosolized Colistin and Gentamicin

INTRODUCTION

Respiratory tract infection leads to a major rate of morbidity and mortality in critically ill patients, especially those on mechanical ventilation (MV) [(1)].

Ventilator-associated pneumonia (VAP) occurred within 48 - 72 hours after endotracheal intubation [(2)]. It is considered as the most common hospital-acquired infection among surgical intensive care unit (ICU) patients [(1)]. The reported incidence of VAP is 8 –28% [(3)]. Also, it is frequently linked to prolonged MV and ICU stays, as well as significant health costs and mortality [(1)].

Pathogens as pseudomonas species, acinetobacter, and methicillin-resistant staphylococcus aureus that can't successfully eradicated by systemic antibiotic (SA) [(1, 4)], alone lead to pneumonia in MV patients, cystic fibrosis or bronchiectasis [(5, 6)].

Current antibiotics for respiratory infection in MV patients are usually limited by multidrug resistant Gram-negative bacteria (MDR-GNB) such as pseudomonas aeruginosa. In addition, eradication of those aggressive bacteria from the airways looks difficult after antibiotic treatment [(7)].

Outcome is often suboptimal, even with antibiotic-susceptible bacterial pneumonia, medical response rates of less than 60% are possible [(8)]. The issue becomes very difficult when bacteria with a minimum inhibitory concentration (MIC) near to the resistance breakpoint are present [(9)]. Increasing the SA dosage increases toxicity. Because nebulized antibiotic treatment directly targets the airways and lung tissue, local concentrations are raised and enhance the effectiveness and reducing the toxicity [(10, 11)].

Many studies have been conducted to investigate the value of inhaled antimicrobial treatment for the prevention of VAP [(12, 13)], as well as an adjuvant to SA for the management of existing VAP [(14, 15)].

The current work was designed to assess the value of aerosolized antibiotics Colistin and Gentamicin in improving the mechanically ventilated patient as adjunctive to intravenous systemic antibiotics.

SUBJECTS AND METHODS

This randomized control (RCT) trial study included a total of thirty mechanically ventilated patients, attending at Respiratory Intensive Care Unit (RICU), Chest Diseases Department, Faculty of Medicine, Ain Shams University Hospitals. This study was conducted between September 2017 to February 2018.

The patients were randomly allocated into three groups:

- Group I: 10 individuals received aerosolized Colistin along with systematic antibiotics (SA).
- Group II: 10 individuals received aerosolized Gentamicin along with SA.
- Group III (Control): 10 individuals received only SA.

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Pregnant women, patients on immunosuppressive therapies other than corticosteroids (except prednisolone at a dosage of 40 mg daily for a duration of > 4 weeks), patients with neutropenia and allergy to the used antibiotics were excluded from this study.

A computer-generated random number list was used for randomization. QuickCalcs was used to build the random number list (GraphPad Software Inc, La Jolla, California).

All participants were subjected to full history taking, clinical assessment, recording of duration of ventilator use, arterial blood gas, complete blood count, renal and liver function tests, C-reactive protein, and chest X-ray using a portable machine.

Sputum culture on day 1 of aerosolized antibiotics was done. All patients were followed up for development of VAP, days of mechanical ventilation, ICU stay, and mortality.

The patient was diagnosed with VAP if there are two of the following clinical criteria with unknown sources of infection: fever (temperature>38°C or <36°C), leukocytosis > 12000/mm3, yellowish, greenish, or purulent sputum production, and sign of a new and persistent radiological infiltration.

***Ethical Consideration*:**

An approval of the study was obtained from Ain Shams University Academic and Ethical Committee. Written informed consent of all the participants was obtained according to Ain shams University Faculty of Medicine's Institutional Review Board. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Continues data was represented as mean and standard deviation (SD), while non numerical data as number and percentage (%). Comparison between groups of categorical classification was performed by chi-square test to find the significant of association. Comparison between groups of numerical data was performed by one way ANOVA test with multiple comparison methods (Tukey test). All statistical tests were two sided, P considered significant if < 0.05.

RESULTS

Patient's characteristics:

The treatment groups were matched as regarding the age and the sex, (P = 0.5 and 0.8) respectively. The comorbidities present were DM; (20 %) of cases in every group, HTN; (30 %) in group I, (20 %) in group II and (10 %) in control group, and IHD which present in group I; (20 %) and control group (50 %). Finally; the primary diagnosis were COPD; (50 %) of cases in group I, (40 %) of cases in group II and (70 %) of cases in control group, and pneumonia; (50 %) of group I, (60 %) of group II and (20 %) of control group. Only one case in group I had Interstitial lung disease (ILD), and 4 cases in control group. Regarding the clinical presentation of the treatment groups; they were matched, as the mean Temp. was around 38°C, and considering the sputum color and amount; 60, 50 and 80 % of cases in the treatment groups had colored sputum respectively, and 60, 90 and 90 % of them had excess amount of sputum, (P = 0.8, 0.4 and 0.4) respectively.

Also, the routine lab of patients showed that; hypoxia and hypercapnia in all groups, also the inflammatory aspect was predominated; increase of TLC and CRP, finally the liver enzymes was elevated too, in the same line, the X-ray finding showed that; (50 %) of group I had X ray shadow at admission, while in group II and control (60 %) and (30 %) of cases had X ray shadow. Sputum culture and sensitivity in group I (20, 30, 20, 10 and 20) % of cases had Klebsiella, acinetobacter, Staph. , E.coli and no growth respectively, in group II (30, 30, 10, 20 and 10) % of cases had Klebsiella, Pseudomonas, acinetobacter, Staph. and no growth respectively, and in control group (30, 30, 10,20 and 10) % of cases had Klebsiella, Pseudomonas, acinetobacter, E. coli and no growth respectively. Finally, 20 % of cases in group I showed resistant to the applied antibiotics, while in group II and control 40 % and 30 % of cases showed resistant to the applied antibiotic respectively **(Table 1).**

Patients' outcomes:

When comparing the treatment groups after 5 days follow up, the temperature in group I showed significant lower degree in comparison with control group, (P= 0.01), while in group II it was not significantly decreased. Also the sputum coloration and excess amount showed insignificant association of particular group than the other, (P= 0.8 and 0.3) respectively. Regarding the other laboratory data, it showed longitudinal improvement in all treatment groups, but with insignificant statistical difference in transverse evaluation. The radiological aspect of cases showed (20 %) of cases in group II with new X ray shadow opposite to (10 %) of cases in control group, with insignificant association of shadow presence with particular group, (P= 0.7). Considering VAP assessment in day 5; in group I no cases had VAP, while in group II and control group, just (20 %) and (10 %) of cases had VAP respectively, with insignificant association of VAP with particular group, (P= 0.3) **(Table 2).**

The mean days of MV and ICU in each groups were (6.8±2.15; 8.9±3.11, 5.9±2.23; 7.2±2.7, 5.1±1.1; 6.1±1.85) respectively, with insignificant statistical difference between the treatment groups, (P = 0.2 and 0.07) respectively. Finally, the survival rate in group I was 90 %, and was slightly lower in group II and control group; 60 % and 50 % respectively, with insignificant association of survival status in particular group, (P = 0.1) **(Table 3).**

Table (1): Patient's characteristics

Variables	Group I (n=10)		Group II (n=10)		Control (n=10)		P
Age (Years), mean/±SD	57.5	9.55	53.7	24.49	61.9	7.37	0.5$
Sex (Male), n/ %	7	70	7	70	8	80	0.8#
Comorbidities, n/%							
DM	2	20	2	20	2	20	1#
HTN (mm Hg)	3	30	2	20	1	10	0.5#
IHD	2	20	0	0	5	50	0.02#
Primary diagnosis, n/%							
COPD	5	50	4	40	7	70	0.4#
Pneumonia	5	50	6	60	2	20	0.2#
ILD	1	10	0	0	4	40	0.04#
Clinical criteria							
Temp, mean/SD	38.2	1.01	38.1	0.7	38.33	0.79	0.8$
Sputum color (colored), n/ %	6	60	5	50	8	80	0.4#
Sputum amount (excess), n/ %	6	60	9	90	9	90	0.4#
Clinical Lab. (mean, SD)							
PH	7.24	0.05	7.28	0.06	7.25	0.13	0.7$
PCO2	79.1	19.9	63.1	20.99	72	24.58	0.3$
PO2	68.4	22.51	65.3	19.44	66.9	22.39	0.9$
HCO3	31.83	8.81	30.43	10.47	31.11	9.21	0.9$
SO2%	83.7	23.09	87.5	10.33	81.87	21.96	0.8$
TLC (mcL)	14.74	7.62	15.95	8.44	32.49	56.82	0.4$
Hb (g/dL)	12.64	2.17	12.38	2.49	13.15	1.82	0.7$
PLT (mcL)	208.3	91.51	222.2	108.12	220.8	115.68	0.9$
Urea (mg/dl)	62.8	44.19	69	45.8	59.7	28.81	0.9$
Creatinine (mg/dl)	1.23	0.41	1.22	0.49	1.29	0.57	0.9$
SGOT (U/L)	43.1	34.59	36.9	21.79	76.2	114.93	0.4$
SGPT (U/L)	62.7	84.92	37.1	31.08	78.1	159.7	0.7$
CRP (mg/L)	53.2	18.47	61	19.24	57.1	26.46	0.7$
X- ray (n, %)							
Shadow	5	50	6	60	3	30	0.4#
Sputum culture (n, %)							
Klebsiella	2	20	3	30	3	30	0.8#
Pseudomonas	0	0	3	30	3	30	0.2#
Acinetobacter	3	30	1	10	1	10	0.4#
Staph	2	20	2	20	0	0	0.3#
E.coli	1	10	0	0	2	20	0.7#
No growth	2	20	1	10	1	10	0.8#
Sensitivity to administered antibiotic (n, %)							
Sensitive	6	60	5	50	6	60	0.6#
Resistant	2	20	4	40	3	30	

$: One way ANOVA test, #: Chi-square test, P considered significant if < 0.05.

Table (2): Comparison between the treatment groups

Variables	Group I (n=10)		Group II (n=10)		Control (n=10)		P
Temp. (mean/±SD)	37.65	0.47	38.15	0.67	38.57	0.83	0.01$
Sputum color (colored), n/ %	6	60	6	60	5	50	0.8#
Sputum amount (excess), n/ %	2	20	5	50	5	50	0.3#
PH (mean/±SD)	7.42	0.03	7.4	0.11	7.4	0.11	0.8$
PCO2 (mean/±SD)	57.5	14.54	44.1	11.06	48.6	12.15	0.07$
PO2 (mean/±SD)	67.4	23.67	75.3	22.86	74.4	20.26	0.7$
HCO3 (mean/±SD)	36.93	8.18	30.05	7.99	32.31	8.14	0.2$
SO2% (mean/±SD)	89.7	6.87	91.8	8.85	92.3	5.56	0.7$
TLC (mean/±SD)	15.12	7.24	15.74	6.39	15.95	8.44	0.9$
Hb (g/dL) (mean/±SD)	13.05	1.94	11.02	1.61	11.85	1.92	0.06$
PLT (mcL) (mean/±SD)	246.5	65.93	223.1	109.13	229.1	123.79	0.8$
Urea (mg/dl) (mean/±SD)	50.59	27.68	56.4	51.29	65	50.25	0.8$
Creatinine (mean/±SD)	4.58	11.39	1.08	0.61	1.19	0.64	0.4$
SGOT (U/L) (mean/±SD)	38.3	19.35	40.9	56.66	34	15.46	0.9$
SGPT (U/L) (mean/±SD)	71.6	85.05	36.9	40.78	74.1	105.68	0.5$
CRP (mg/L) (mean/±SD)	40.8	12.05	42.1	20	45	18.66	0.8$
X- ray (n/%)							
New shadow	0	0	2	20	1	10	0.7#
VAP assessment in day 5 (n/%)							
Present	0	0	2	20	1	10	
Absent	10	100	8	80	9	90	0.3#

$: One way ANOVA test, #: Chi-square test, P considered significant if < 0.05.

Table (3): Outcome of the treatment groups as regarding duration of MV (day), duration of ICU (day) and survival status

Variables	Group I (n=10)		Group II (n=10)		Control (n=10)		P
MV duration (day) (mean/±SD)	6.8	1.15	5.9	11.23	5.1	1.1	0.2$
Total ICU duration (day) (mean/±SD)	8.9	2.11	7.2	1.7	6.1	1.85	0.07$
Survival status (n, %)							
Survived	9	90	6	60	5	50	
Died	1	10	4	40	5	50	0.1#

$: One way ANOVA test, #: Chi-square test, P considered significant if < 0.05.

DISCUSSION

The current RCT study was conducted to assess the efficacy of aerosolized antibiotics Colistin and Gentamicin in improving the mechanically ventilated patient as adjunctive to intravenous systemic antibiotics. Regarding the morphological description of the groups; they were matched as regarding the age, sex, most of co morbidities (DM and HTN) and diagnosis (COPD and pneumonia) (P = 0.5, 0.8, 1, 0.5, 0.4 and 0.2) respectively. The comorbidities present were DM; (20 %) of cases in every group, HTN; (30 %) in group I, (20 %) in group II and (10 %) in control group, and IHD which present in group I; (20 %) and control group (50 %). Finally; the primary diagnosis was COPD; (50 %) of cases in group I, (40 %) of patients in group II and (70 %) of cases in controls, and pneumonia; (50 %) of group I, (60 %) of group II and (20 %) of controls.

Only one case in group I had ILD, and 4 cases in controls. This primary diagnosis came in consistence with **Ali** [16] study, who discussing the effect of aerosolized antibiotic beside the systematic one and developing VAP or Ventilator-associated tracheobronchitis (VAT); he found that; the most common primary diagnoses at admission was chronic obstructive pulmonary disease (COPD) (30.43%), also in agreement with **Nseir *et al.*** [17]**,** who carried out a multi-centric study in Spain, Greece, and France on the transition from VAT to VAP. On the other hand, **Palmer *et al.*** [18] disagreed as he found that among the forty-three critically ill patients who developed VAT in the general ICU, the abdominal infection and cardiac problems were commonest primary diagnosis and that may be due to different ICU types.

The incidence of VAP in the current work was (10%), most of them present in group II (6.6%) and the

rest in control group with mean age 55 years and SD about (33.1), 66.67% of them were male, in concordance with **Nseir *et al.* [17],** they investigated thirty patients in surgical and medical ICUs and found VAT rates of 15.3% and 11.2%, respectively. On the other hand, **Ali [16]** study reported a higher incidence (22.1%) while **Dallas *et al.* [19],** observed a reduced VAT rate of 1.4 and 4% in surgical and medical ICUs, respectively. This discrepancy might be attributed to the varied methods used for sputum sample in those studies. Furthermore, sampling was done weekly or if trachea bronchitis was suspected; additionally, cultures were positive at larger than 105 CFU/ml, which raised the potential of missing microorganisms in low amount during VAT. All of these variables might lead to an under or overestimation of VAT.

Regarding the clinical and radiological presentation of the treatment groups at the begging of the study; they matched, as the mean temperature was around 38^{O}C, the colored sputum and excess amount present in (60, 50 and 80 %) and (60, 90 and 90 %) of patient's groups respectively, (P = 0.8, 0.4 and 0.4) respectively. Also, the studied groups were matched as regarding X-ray finding; (50 %), (60%) and (30%) had X-ray shadow at admission respectively, (P = 0.4). After 5 days of application of nebulizer antibiotics, the temperature in group I showed significant lower degree in comparison with control group, (P= 0.01), while in group II the temperature was not significantly decreased, also no new X ray shadow in group I and (20 and 10 %) had new X ray shadow in group II and control group respectively, that mean the nebulizer by colistin could protect the patients from developing VAP.

The clinical findings of the current work were compatible with **Ali [16] and Craven *et al.* [20]** studies that involved 188 mixed ICU patients with intubation for >48 hour in which VAT was diagnosed based on the presence of at least 2 clinical criteria (fever, leukocytosis, or purulent sputum). In the same line, the study of **Montgomery *et al.* [21] and Rodriguez *et al.* [22]** agreed with the present work and the later revealed that VAT incidence was 79.2% based on clinical and microbiological criteria. In comparing the clinical outcome of the present study; recording VAP at the 5th day of assessment, by both radiological morphology (new shadow in X-ray) and clinical changes in patient's sputum, **Ali [16]** observed the same finding, as he found a significant decrease in temperature, on D5 compared with day 1 (P=0.005) in group I, whereas group II showed no significance between D1 and D5; clinical enhancement was 80% in group I and 30% in group II.

Also, in agreement with **Palmer *et al.* [18]**, they investigated the efficacy of aerosolized antibiotics (AAs) on respiratory tract infections (RTI) in MV patients and discovered that signs of RTI dropped from 73.6% on D1 to 35.7% in 14 days therapy, compared to 75% and 78.6% in the placebo, respectively. On the same line **Lu *et al.* [23],** who did a CRT of aerosolized antibiotics in participants with VAP due to P. aeruginosa and revealed that enhancement in VAP was reported in 70% of inhaled ceftazidime and amikacin plus SA group compared with 55% of the controls who received SA alone. Another two studies agreed with us; **Niederman *et al.* [24]**, who revealed that clinical enhancement in VAP was observed in 94% of the inhaled amikacin plus SA group compared with 88% of the controls, and **Ali [16]**, who evaluated eighteen patients with VAP, the clinical enhancement was observed in the group that received aerosolized amikacin and ceftazidime plus SA when compared with the group that did not receive AAs.

The secondary outcome of the present work includes; MV period, length of stay in ICU and survival status, we reported that; the mean days of MV and ICU in each groups were (6.8±2.15; 8.9±3.11, 5.9±2.23; 7.2±2.7, 5.1±1.1; 6.1±1.85) days respectively, with insignificant statistical difference between the treatment groups, (P = 0.2 and 0.07) respectively. Finally, the survival rate in group I was 90 %, and was slightly lower in group II and control group; 60 % and 50 % respectively, with insignificant association of survival status in particular group, (P = 0.1).

Considering the MV period, the present results came in concordance with **Ali [16]** as she found no significant reduction in mechanical ventilation days in group I when compared with group II (P=0.14), the same results founded in **Palmer *et al.* [18]**, and **Palmer and Smaldone [25],** studies, the later founded that, mean of ventilator days was lower in the aerosolized antibiotics group but not significant; (AA group, 19.9±2.1; placebo, 13.5±2.1). As regards total ICU stay days, **Ali [16]** agreed as she found that group I showed no significant reduction in ICU stay days when compared with group II (P=0.178). The present results matched also with **Wood *et al.* [26],** who studied a fifty-nine critically ill trauma patients with VAP length of stay was 11 days in the ceftazidime plus SA group in comparison with 12 days in the controls.

Regarding mortality status, **Ali [16]** found the same finding of our study that no significance between group I and group II (P=1), in the same line **Ioannidou *et al.* [27] and Palmer *et al.* [18]**, they found that mortality rate in the AA group and the controls didn't differ significantly. **Lu *et al.* [11]** also agreed, they carried out a study comparing the efficacy of nebulized colistin in treating forty-three VAP patients infected with MDR Gram-negative pathogens to parenteral antibiotic therapy, and discovered that death rate was not different between groups. The present study disagrees with **Doshi *et al.* [28]**, who carried out a research in which they compared intravenous colistin to aerosolized and intravenous colistin in twenty-four individuals. They noted that the intravenous group indicated a trend toward increased mortality (70.4 vs. 40.7%). The discrepancy might be attributed to

differences in the primary diagnosis upon admission, the existence of comorbidities, their response to therapy, and the organisms' susceptibility to the antibiotics administered.

CONCLUSION

It could be concluded that the incidence of VAP in the RICU in Abbassia Chest Hospital was 10% and the empirical treatment by AA (Colistin) was effective as an adjuvant to SA for protection of VAP than aerosolized Gentamicin, it had better improvement of respiratory infection, and subsequently the MV days, ICU stay days and cost, however, mortality rate not affected.

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