Benha Journal of Applied Sciences (BJAS) **print : ISSN 2356–9751**
Vol.(4) Issue(1) (2019), xxx-xxx **online : ISSN 2356–976x**
http:// bjas.bu.edu.eg

The Efficacy and Safety of using Nebulized Antibiotics in Treatment of Ventilator-Associated Pneumonia

O.S.Arafa[1], T.S.Essawy[2] , B.M.Aglan[3] and E.A.Attaya[4]
[1]Cardiology Dept., Faculty of Medicine, Benha Univ., Benha, Egypt
[2]Chest Dept, Faculty of Medicine, Benha Univ., Benha, Egypt
[3]Cardio thoracic Dept, Faculty of Medicine, Benha Univ., Benha, Egypt
[4]Critical Care Dept, Faculty of Medicine, Benha Univ, Benha, Egypt
E-Mail:Emad.ata23@yahoo.com

Abstract

Development of ventilator- associated pneumonia [VAP] is associated with high morbidity and mortality rates. VAP mortality ranges between 5.8% and 27% [1]. Routine administration of intravenous antibiotics does not reach a bactericidal concentration in lung tissues. intravenous antibiotics are mainly detected in respiratory segments of lungs, but not in sputum [2]**.**This study was conducted on 60 patients who were admitted to critical care department at Benha University Hospital and diagnosed with Ventilator Associated Pneumonia [VAP]. patients were divided into two groups: Group A included 30 patients have received only systemic antibiotics and Group B included 30 patients have received systemic and nebulized antibiotics. In this study the clearance of organism, resistance, superinfection and combined [resistance and super infection] were significantly different in group A vs.B .There was significant decrease regarding creatinine level in group B vs. A .There were significant reduction in duration of MV and length of ICU stay in group B vs. A.Nebulized Amikacin plus ceftazidime are effective in the treatment of VAP.

1.Introduction

The incidence of VAP is approximately 10%-30% of patients required mechanical ventilation for more than 48 h. This incidence depends on the type of population studied, risk factors, and the quality of preventive protocols implemented [3] .

The mortality rate for VAP exceeds that of death due to infections associated with central venous catheters, severe sepsis, and respiratory infections in non-intubated patients [4].

The US National Healthcare Safety Network - Centers for Disease Control and prevention have an algorithm for defining healthcare-associated pneumonia Table **(**1).

1.1Radiological signs

Two serial chest x-rays with one or more of the following:-

– New or progressive and persistent infiltrate
– Cavitation
– Consolidation

1.2Clinical signs

I- At least one of the following

– Fever [temperature >38 °C] with no other recognised cause
– Leucopaenia [<4.0 × 109 cells/L] or leukocytosis [>12.0 × 109 cells/L]
– For adults >70 years of age, altered mental status with no other recognised cause

II-And ≥ two of the following

– New onset of purulent sputum, change in character of sputum,
– Increased respiratory secretions, or increased suctioning requirements
– New-onset or worsening cough, or dyspnoea, or tachypnoea
– Rales or bronchial breath sounds
– Worsening gas exchange, eg oxygenation index ratio [PaO2/FiO2] ≤240, increased oxygen requirement, or increased ventilation demand

In Egypt, 17 studies searching the causative organisms of VAP stated that: the most common pathogens causing VAP from all these studies were Pseudomonas aerogenosa, Klebsiella, Escherichia coli, Staphylococcus.aureus, Acinetobacter, Candida and Proteus [6] .

Many strategies have been evaluated in order to decrease the incidence of VAP. Decreasing the intubation time, care of oral cavity and endotracheal tube, positioning, and adequate feeding are important items in prevention of VAP. Many of these strategies were incorporated into 'VAP bundles', a set of management protocols have been implemented to reduce VAP incidence [7].

When VAP is clinically suspected, an appropriate antimicrobial therapy should be immediately started as both delayed or inadequate treatment have been associated with increased rates of morbidity and mortality. However, overuse of antimicrobial drugs leads to some undesirable treatment-related complications and costs, and increases the microbial resistance [5],[8] **.**

The inhaled antimicrobial agents achieved 200-time greater concentration in the respiratory tract secretions than levels achieved in the blood. In comparison to systemic therapy with the same antimicrobials, nebulized therapy achieved much higher

sputum concentrations with less systemic toxicity [9].

Inhaled antibiotics reach high concentrations in respiratory secretions, are absorbed through the bronchial epithelium, and are distributed by well-developed sub-mucosal capillaries to the lung parenchyma. [10]

2.Patients and methods

This study was conducted on 60 patients who were admitted to critical care department at Benha University Hospital and diagnosed with Ventilator Associated Pneumonia [VAP]. patients were divided into two groups:

- **Group [A]** included 30 patients: Patients received the conventional intravenous antibiotics only according to sputum culture and sensitivity without any nebulized antibiotics for five days of treatment followed by EET (endotracheal tube) or BAL (Bronco Alveolar Lavage) aspiration and sent for culture and sensitivity .
- **Group [B**] included 30 patients: Patients received nebulized ceftazidime [15 mg/kg/3h diluted with 4 ml of sterile normal saline] plus nebulized amikacin [25 mg/kg/d diluted with 4 ml of sterile normal saline] in addition to the conventional treatment regimen of intravenous antibiotics according to culture and sensitivity for five days of treatment. followed by EET or BAL aspiration and sent for culture and sensitivity.

3.Results

There were no significant differences between both groups as regard age, gender, co-morbidities or cause of admission as shown in Table (1)

Table (1) Demographic characteristics, Co-morbidities and causes of admission in both groups

			Group A [n = 30]	Group B [n = 30]	P value
Demographic characteristics	**Age [years]**	Mean ±SD	54 ±4	54 ±3	0.839
	Sex	Males n [%]	20 [66.7%]	19 [63.3%]	0.787
		Females n [%]	10 [33.3%]	11 [36.7%]	
Co-morbidities	**DM**	n [%]	20 [66.7%]	18 [60.0%]	0.592
	HTN	n [%]	16 [53.3%]	19 [63.3%]	0.432
Causes of admission	**Neurological**	n [%]	13 [43.3%]	12 [40.0%]	0.793
	Respiratory	n [%]	30 [100.0%]	30 [100.0%]	NA

Although there were no significant differences between both groups as regard pre-treatment diagnostic criteria of temperature, PaO_2/FiO_2 and total leukocytic count [TLC], the Post-treatment mean temperature was significantly higher in group A compared to group B and other values were without significant difference as shown in Table (2).

Table (2) pre and post treatment diagnostic criteria in both groups

			Group A [n = 30]	Group B [n = 30]	P value
Temperature	**Pre treatment**	Mean ±SD	38.6 ±0.6	38.4 ±0.3	0.143
	Post treatment	Mean ±SD	37.8 ±0.7	37.2 ±0.5	<0.001
PaO_2/FiO_2	**Pre treatment**	Mean ±SD	170 ±43	191 ±75	0.193
	Post treatment	Mean ±SD	182 ±34	201 ±44	0.077
TLC	**Pre treatment**	Mean ±SD	14 ±3.3	16.2 ±5.2	0.061
	Post treatment	Mean ±SD	11.4 ±2	11.5 ±5.7	0.948

Organisms revealed from cultures before treatment involved different pathogens. Acinetobacter organism was more common in group A [36.7%] and was significantly higher compared to group B [10.0%]. P value was 0.015. Other organisms included Pseudomonas [26.7%] in group A and [43.3%] in group B, Klebsiella [20.0%] in group A and [36.7%] in group B, and others with no significant difference between both groups.

Looking at the post-treatment outcome in both groups, there was a significant difference between both groups with better outcome for group A as regard organism clearance, duration of mechanical ventilation and length of hospital stay. There was no significant difference between both groups as regard

Clinical Pulmonary Infection Score or mortality as shown in Table (3).

Regarding drug complications,no bronchospasm was reported in both groups. Post-treatment mean creatinine was significantly higher in group A [1.3] compared to group B [0.9]. P value was 0.01.

Table (3) Post treatment outcome in both groups

		Group A [n = 30]	**Group B [n = 30]**	**P value**
Organism clearance	No growth	15 [50.0%]	21 [70.0%]	0.03
	Resistance	6 [20.0%]	2 [6.7%]	
	Resistance and super infection	4 [13.3%]	7 [23.3%]	
	Super infection	5 [16.7%]	0 [0.0%]	
CPIS score	<6	16 [53.3%]	22 [73.3%]	0.108
	>6	14 [46.7%]	8 [26.7%]	
Duration of MV [days]	Mean ±SD	24 ±5	19 ±2	<0.001
Length of hospital stay [days]	Mean ±SD	24 ±4	22 ±3	0.025
ICU mortality	n [%]	24 [80.0%]	18 [60.0%]	0.091

4.Discussion

Aerosol antibiotics as a local treatment are very useful since they can deliver locally to the infection site less volume of drug in efficient concentrations. The major advantage of the local treatment in the respiratory infection is that we bypass the "first-pass"metabolism and we have less systemic adverse effects.

In the present study, we have evaluated the efficacy and safety of nebulized Ceftazidime plus Amikacin as an adjunctive to IV antibiotics in treatment of VAP during ICU stay.

Regarding the microbiological outcome after treatment, There was a significant difference between both groups as regard organism clearance. clearance of organisms was [50% vs 70%, p 0.03], resistance was [20% vs. 6.7%] and superinfection was [16.7% vs. 0.0%,] in group A vs. B respectively.

Similar results were reported by A.Torres et al. [3] **,** Patients treated with inhaled antibiotics were more likely to have complete resolution of microbiologic infection [77% vs 8% in the intravenous antibiotic group: P < 0.0006].

A.C.Morris et al. [7] used nebulized Ceftazidime plus Amikacin for 8 days without IV adjunctive antibiotics without statistically significant difference between IV and nebulization groups.

In the study by L.B.Palmer et al. **[9],** showed that inhaled antibiotics can eradicate a chronic pool of MDRO found in the sputum of patients in the intensive care unit [ICU]. These effects were demonstrated in a typical tertiary care ICU environment in a population of patients difficult to wean while receiving numerous courses of antibiotics .

4.1Duration of MV and length of ICU stay [days]

- Mean duration of MV was significantly higher in group A [24 days] compared to group B [19 days]. P value was <0.001
- Mean length of hospital stay was significantly higher in group A [24 days] compared to group B [22 days]. P value was 0.025

In the study by V.L.Yu et al. [8], showed a much longer period in which the median of days of MV was 29 day in while LOS was 38 day in nebulized group without significant differences in comparable to control group [p 0.8] .

In the study by A.Fathy et al. [6], showed that Total ventilator days were decreased with inhaled antibiotics but not significantly [13.5 ± 2.1vs 12.9 ± 2.1 ; *P* = 0.078] **.**

In the study by A.McCullagh et al. [10],showed that Mean duration of MV was 22days in nebulized group without significant differences in comparable to control group 25 days .

The definition of a prolonged ICU stay varies by hospital type, ICU type, and also different diseases L.B.Palmer et al. [9], ICU LOS and days of MV known to be influenced by several factors; medical severity factors, psychosocial factors, medical complications, degree of disability and institutional factors .

4.2 Complications [renal impairment and bronchospasm]

Pre-treatment, there was no significant difference between both groups. P value was 0.092

Post treatment, mean creatinine was significantly higher in group A [1.3] compared to group B [0.9]. P value was 0.01. No bronchospasm was reported in both groups.

V.L.Yu et al. [8], similarly showed that there was no bronchospasm during nebulization, while there was no significant difference between nebulized group and control as regard creatinine levels.

In the study by [6], showed that Nephrotoxicity was monitored by serial creatinine assessment. no significant difference was seen [mean ± SD, randomization, 0.79 ± 0.55; end of study, 0.73 ± 0.44; $P = 0.50$ vs randomization, 0.84 ± 0.73; end of study, 0.93 ± 1.26; $P < 0.67$] .

In the study by [4] ,showed that there were no serious adverse events associated with inhaled antibiotics. Patients who received these antibiotics intravenously developed renal dysfunction [31%]; none of the patients treated with inhaled antibiotics developed nephrotoxicity [P < or = 0.04]. no bronchoconstriction or apnea.

4.3Outcome and mortality

In group A mortality was 80% versus 60% in group B. There was no significant difference between both groups as regard ICU mortality. P value was 0.091.

A remarkably lower mortality rate was reported by the A.Fathy et al. [6], mortality rate in nebulized group was 10% versus 5% in IV group, without significant differences [p 0.55].

The population study In[6] may not be entirely representative of the population of patients with VAP since some selection criteria may have introduced a potential bias by treating only one type of organism [*pseudomonas*]. Moreover 20% of patients with *P. aeruginosa* VAP had positive blood cultures and have been excluded in the study, which represent the severe forms of septic patients with a high potential mortality.

In the study by by A.McCullagh et al. [10] **,** showed that Mortality differences were not significant [2 of 18 vs 6 of 24] . Deaths were the result of multiorgan system failure.

In the study by L.B.Palmer [9] ,showed that Patients treated with inhaled antibiotics were more likely to have complete resolution of clinical [81% vs 31% in the intravenous antibiotic group; P < 0.01] and microbiologic infection [77% vs 8% in the intravenous antibiotic group: P < 0.0006].. In critically ill patients with Gram-negative VAP, inhaled aminoglycosides were tolerated without serious toxicity and may lead to improved outcome.

4.4 Clinical cure

In group A the clinical cure [CPIS scoring<6] was 53.3% versus 73.3% in group B .

There was no significant difference between both groups as regard Clinical Pulmonary Infection Score [CPIS]. P value was 0.108

This is similar to the study done by L.B.Palmer et al. [9], the clinical cure was 55% versus 70% without significant differences [p 0.33].

A.McCullagh et al. [10] , showed that favorable outcome was 51% in nebulized group versus 53% in control group without significant differences [p 0.84].

L.B.Palmer et al. [9], showed that Treatment with nebulized antibiotics was associated with a significant drop in CPIS suggesting a low post-treatment risk for deep lung infection.

In another study done by V.L.Yu et al [8], it shows clinical cure rate was 66% in sensitive strain group and 67% in multidrug-resistant strain group without significant differences.

Despite that the clinical cure rate in nebulized groups was higher there were no statistically significant differences, may be due to the low sample size in the previous studies.

One potential explanation for the disparate results involves the antibiotic nebulization technique. Achieving adequate treatment of any pulmonary infection via inhaled antibiotics requires delivery of sufficient antibiotics to the lungs. This involves adequate nebulization of the antibiotics into appropriate particle size for delivery in high concentrations. Previous researches demonstrate that certain types of nebulizers [e.g. jet nebulizers] may be less efficient at antibiotic delivery than other methods [e.g ultrasonic or vibrating plate nebulizers] for patients on mechanical ventilation . Thus, differences seen in efficacy of inhaled antibiotics may be due to differential delivery of antibiotics to the target tissue .

5.Recommendation

Nebulized Amikacin plus ceftazidime are effective in the treatment of VAP.

Large studies are needed for evaluating the efficacy and safety of nebulized antibiotic in treatment of VAP and the possibility of their use as prophylactic and empirical stand-alone therapies, thus minimizing systemic antibiotics side effects and toxicity.

References

[1] J.Valles, A.Pobo, O.Garcia-Esquirol, Excess ICU mortality attributable to ventilator-associated pneumonia: the role of early vs. late onset. Intensive Care Med, Vol.33,PP.1363-1368,2007.

[2] N.Hoiby, Recent advances in the treatment of Pseudomonas aeruginosa infections in cystic fibrosis. BMC Med, Vol.2,PP.9-32,2011.

[3] A.Torres, M.Ferrer and J.R.Badia, Treatment guidelines and outcome of hospital acquired and ventilator associated pneumonia. Clinical Infectious Disease, Vol.51,PP.48-53,2010.

[4] M.Restrepo, A.Anzueto and A.Arrogliga, Economic burden of ventilator-associated pneumonia based on total resource utilization. Infect. Control Hosp. Epidemiol., PP.31:509-515,2010.

[5] T.Horan, M.Andrus, M.Dudeck, CDC/NHSN surveillance definition of health care–associated infection and criteria for specific types of infections in the acute care setting. Am J Infect. Control, Vol.36,PP.309-32,2008.

[6] A.Fathy, R.Abdelhafeez , A.EL-Gilany , Analysis of ventilator associated pneumonia [VAP] studies in Egyptian University Hospitals Egyptian Journal of Chest Diseases and Tuberculosis, Vol.62,PP.17–25,2013.

[7] A.C.Morris, A.W.Hay, D.G.Swann, Reducing ventilator-associated pneumonia in intensive care: Impact of implementing a care bundle. Crit Care Med, Vol.39,PP.2218-2224,2011.

[8] V.L.Yu, N.Singh, Excessive antimicrobial usage causes measurable harm to patients with suspected ventilator-associated pneumonia. Intensive Care Med, Vol.30(5),PP.735–738,2004.

[9] L.B.Palmer, G.C.Smaldone, J.J.Chen, Aerosolized antibiotics and ventilator-associated tracheobronchitis in the intensive care unit. Crit. Care Med,Vol.36,PP.708-712,2013.

[10] A.McCullagh, M.Rosenthal, A.Wanner, The bronchial circulation - worth a closer look. Pediatr. Pulmonol., PP. 45, 1-13,2010.