Effectiveness of Adjunctive Inhaled Colistin in Treatment of Ventilator Associated Pneumonia

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ABSTRACT

Ventilator-associated pneumonia (VAP) represents a major health problem in mechanically ventilated patients in intensive care units (ICUs). Aerosolized colistin could represent an adjunctive treatment to intravenous antibiotics in VAP. To evaluate the safety and efficacy of adjunctive inhaled colistin in treatment of patients with Gram-negative VAP compared to the conventional intravenous antibiotic regimen alone. This prospective randomized controlled study was conducted from July 2013 to August 2014 at Kasr El-Aini Medical ICU. Our study included a total number of 50 cases with VAP randomly assigned into two equal groups; a study group (who received the conventional systemic IV antibiotic regimen plus adjunctive inhaled colistin) and a control group (who received the conventional systemic IV antibiotic regimen alone). 76% of the patients were men with severe underlying co-morbidities. The main causative organisms of VAP were Klebsiella spp. (32%), Acinetobacter spp. (26%) and Pseudomonas spp. (24%). Patients in the study group had significantly more favourable microbiological outcome when compared with patients in the control group (80% versus 52%, P=0.03). No adverse effects related to inhaled colistin (nephrotoxicity, neurotoxicity, bronchoconstriction, cough, apnea or chest tightness) were recorded. Inhaled colistin seems to be safe and efficient as an adjunctive treatment for patients with Gram-negative VAP.

Keywords: Ventilator-associated pneumonia (VAP), Inhaled colistin, Intensive care unit (ICU).

INTRODUCTION

Concerns about the use of aerosolized antibiotics in the treatment of ventilator associated pneumonia (VAP) are increasing in modern medicine. VAP frequently complicates the clinical course of patients admitted to intensive care units (ICUs) for multiorgan failure. Early intravenous administration of appropriate antibiotics is considered as a prerequisite for an efficient treatment of VAP, and bacteriological identification of the causative microorganisms is the only way to limit the unnecessary use of antibiotics in the ICU. Lung penetration of intravenous antibiotics is, however, often limited; despite appropriate initial antibiotics administration, treatment failure is not infrequent, leading to increased dosage, risk of systemic toxicity and prolongation of administration. Inappropriate antibiotic concentration at the site of infection and increased antibiotic exposure within the ICU represent important risk factors for development of VAP with resistant organisms. Aerosolized antibiotics could represent an attractive alternative to intravenous antibiotics with numerous potential advantages. Reaching the deep lung through the tracheobronchial tree should allow a better control of the main source of parenchymal infection and bronchial colonization. Bypassing the alveolar-capillary barrier should provide high antibiotic concentrations at the site of infection if enough aerosolized particles are delivered to the deep lung. A reduction of the risk of systemic toxicity should be expected because antibiotic diffusion from bronchial and alveolar compartments to the systemic circulation is restricted by the presence of difficult-to-cross physiologic barriers (bronchial wall and alveolar–capillary barrier). Aerosolized colistin might be an alternative option for treatment of patients with VAP because the drug achieves high concentration in the respiratory tract while avoiding systemic effects. Colistin (or polymyxin E) is an old antibiotic extracted from different species of Bacillus polymyxa in the decade of 1940s and was extensively used parenterally for more than two decades. Subsequently, polymyxins were gradually withdrawn from clinical practice for many years owing to reports of nephrotoxicity and neurotoxicity. The re-introduction of polymyxins in clinical practice during the last years was the result of the increased resistance rates among Gram-negative bacteria, especially in the ICU.
setting, and the absence of new and effective alternative therapeutic options\textsuperscript{10}. Aerosolized colistin is effective in preventing relapses of lung infections\textsuperscript{11}. It is used also as a supplementary therapy to the conventional intravenous antibiotic therapy for the treatment of nosocomial or ICU-acquired pneumonia caused by MDR Gram-negative microorganisms with good results\textsuperscript{12,13}. Aerosolized colistin has been recommended in the American Thoracic Society Guidelines as a therapeutic option for the treatment of VAP caused by Gram-negative organisms\textsuperscript{14}.

The aim of the present work was to evaluate the safety and efficacy of adjunctive inhaled colistin in treatment of patients with Gram-negative VAP compared to conventional intravenous antibiotic regimen alone.

**MATERIALS & METHODS**

This prospective randomized controlled study was conducted from July 2013 to August 2014 at Kasr El-Aini University Hospital, Medical Intensive Care Unit, Faculty of Medicine, Cairo University. Our study included a total number of 50 cases of VAP. An informed consent was obtained from all participating patients or their legal representatives.

**I) Inclusion criteria:**
- Patients admitted to the ICU requiring intubation and mechanical ventilation for $\geq 48$ hours with a confirmed diagnosis of Gram-negative VAP which was judged not to have been incubating before the initiation of mechanical ventilation.

**II) Exclusion criteria:**
- Age $< 18$ yrs old.
- Severe renal impairment.
- Severe asthma.
- Irreversible shock states.

➢ **Enrolled patients were randomly assigned into two groups:** as shown in the study flow diagram (Figure 1)

**A) Study group:**
- This group included 25 patients with VAP who received the conventional systemic IV antibiotic regimen plus adjunctive inhaled colistin methanesulfonate (CMS) regimen.

**B) Control group:**
- This group included 25 patients with VAP who received the conventional systemic IV antibiotic regimen alone.

**Fig. (1): Study flow diagram**

➢ **Diagnosis of VAP caused by Gram-negative bacteria was established on the basis of both Clinical and Microbiological criteria:**

1) Johanson clinical criteria were used in diagnosing VAP\textsuperscript{15}. These criteria were also recommended by the American Thoracic Society Consensus Conference on VAP\textsuperscript{14}.

- Presence of a new or progressive radiographic pulmonary infiltrate.
- Plus at least two of three clinical features:
  - Fever $> 38^\circ\text{C}$.
  - Leukocytosis (WBCs $\geq 12,000$ cells/mm$^3$) or leucopenia (WBCs $\leq 4,000$/mm$^3$).
  - Purulent secretions.

2) Microbiological criteria:
- Culture of the aspirate from the endotracheal tube (ETT) and only culture’s results with Gram-negative bacteria were included in our study.

➢ **VAP treatment regimens:**

1) Intravenous conventional antibiotic(s) regimen:
- Upon Suspicion of VAP:
  Empirical intravenous antibiotic regimen was chosen initially according to the antibiotic policy coinciding with the hospital biogram recommendations and as recommended by the guidelines of the *ATS and IDSA*\textsuperscript{14} according to the time of onset of VAP.
2) Inhaled colistin (CMS) regimen:
One million IU of CMS was delivered every 8 hours (3 million IU/day) via a jet nebulizer, immediately after reconstitution in 4ml of saline, for a period of 5 days after confirming the diagnosis of Gram-negative VAP by culture and sensitivity

➢ Assessment of effectiveness of treatment regimens with one of the following possibilities by taking another sample on day 5 for culture and sensitivity:
1) Clearance of the causative pathogen was defined as no growth after 48 hours incubation.
2) Clearance of the causative pathogen with emergence of a new one.
3) Clearance of one organism and persistence of the other one in case of multiple causative organisms.
4) Persistence of the pathogen was defined as persistent growth of the causative pathogen.
5) Persistence of the causative pathogen and emergence of a new one.

➢ Assessment of safety of treatment regimen and occurrence of complications:
1) Follow up of the patients for occurrence of renal impairment was done by renal function tests. Normal renal function was defined as a serum creatinine level of ≤1.2 mg/dl. Acute renal failure was defined as a rise of 2 mg/dl in the serum creatinine level of patients with previously normal renal function. In patients with a history of renal insufficiency, acute or chronic renal failure was defined as at least a doubling of the baseline serum creatinine level (defined as the creatinine level at the time of initiation of colistin treatment)⁹⁰.
2) All potential adverse effects related to the inhaled antibiotic such as neurotoxicity, bronchoconstriction, cough, apnea, or chest tightness were recorded.

➢ Statistical Analysis:
All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and IBM SPSS Advanced Statistics version 20.0 (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) for Microsoft Windows. Chi-square test (Fisher’s exact test) was used to examine the relation between qualitative variables. For quantitative data, comparison between two groups was done using Mann-Whitney test. A probability value (p-value) <0.05 was considered statistically significant.

RESULTS
1) Age and Sex Distribution in study and control groups:
In the present study, 76% of the patients were men as shown in table (12). The study group included 25 patients with mean age (52.4±17.2), 19 (76%) males and 6 (24%) females. The control group included 25 patients with mean age (53.6 ± 18.6), 19 (76%) males and 6 (24%) females. There was no statistically significant difference in age or sex between both groups.

Table (1): Age and Sex Distribution in study and control groups.

<table>
<thead>
<tr>
<th>Age and Sex</th>
<th>Study (n=25)</th>
<th>Control (n=25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>19 (76%)</td>
<td>19 (76%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Females</td>
<td>6 (24%)</td>
<td>6 (24%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Mean age ±SD (years)</td>
<td>52.4±17.2</td>
<td>53.6 ± 18.6</td>
<td>0.89</td>
</tr>
</tbody>
</table>

2) Indications for mechanical ventilation in study and control groups
In the present study, most of the patients presented with severe underlying co-morbidities as shown in table (2). Neurological causes and head trauma represented (56% vs. 60%), Respiratory causes represented (28% vs. 40%), Cardiac causes represented (4% vs. 0%) and Hepatic causes (12% vs. 0%) in study vs. control groups respectively.

Table (2): Indications for mechanical ventilation in study and control groups.

<table>
<thead>
<tr>
<th>Co-morbidities</th>
<th>Study (n=25)</th>
<th>Control (n=25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological</td>
<td>14 (56%)</td>
<td>15 (60%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Respiratory</td>
<td>7 (28%)</td>
<td>10 (40%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Hepatic</td>
<td>3 (12%)</td>
<td>0</td>
<td>0.24</td>
</tr>
<tr>
<td>Cardiac</td>
<td>1 (4%)</td>
<td>0</td>
<td>1.0</td>
</tr>
</tbody>
</table>
3) Causative organisms of VAP from initial culture in study and control groups:

In the present study, the initial causative organisms were: Klebsiella spp. (48% vs. 16%, \(P=0.02\), Acinetobacter spp. (20% vs. 32%), Pseudomonas spp. (12% vs. 36%), multiple growth (Klebsiella & Pseudomonas) represented (12% vs. 4%), multiple growth (Klebsiella & Acinetobacter) represented (4% vs. 4%), E.Coli (4% vs. 0%), Citrobacter spp. (0% vs. 4%), Proteus spp. (0% vs. 4%) in study vs. control groups respectively.

Table (3): Causative organisms of VAP from the initial culture in study and control groups

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Study (n=25)</th>
<th>Control (n=25)</th>
<th>(P) value</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klebsiella spp.</td>
<td>12 (48%)</td>
<td>4 (16%)</td>
<td>0.02</td>
<td>32%</td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td>5 (20%)</td>
<td>8 (32%)</td>
<td>0.54</td>
<td>26%</td>
</tr>
<tr>
<td>Pseudomonas spp.</td>
<td>3 (12%)</td>
<td>9 (36%)</td>
<td>0.12</td>
<td>24%</td>
</tr>
<tr>
<td>Multiple growth (Klebsiella &amp; Pseudomonas)</td>
<td>3(12%)</td>
<td>1(4%)</td>
<td>0.49</td>
<td>8%</td>
</tr>
<tr>
<td>Multiple growth (Klebsiella &amp; Acinetobacter)</td>
<td>1(4%)</td>
<td>1(4%)</td>
<td>1.0</td>
<td>4%</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>1 (4%)</td>
<td>0</td>
<td>1.0</td>
<td>2%</td>
</tr>
<tr>
<td>Citrobacter spp.</td>
<td>0</td>
<td>1 (4%)</td>
<td>1.0</td>
<td>2%</td>
</tr>
<tr>
<td>Proteus spp.</td>
<td>0</td>
<td>1 (4%)</td>
<td>1.0</td>
<td>2%</td>
</tr>
</tbody>
</table>

MDR organisms (30% Acinetobacter spp. and 6% Pseudomonas spp.) represented [7 (28%) vs. 11 (44%), \(P=0.38\)] in study vs. control groups respectively. Patients who developed VAP caused by multiple organisms represented [4 (16%) vs. 2 (8%), \(P=0.53\)] in study vs. control groups respectively.
4) Microbiological outcome after 5 days of treatment in study and control groups:

In the present study, patients in the study group had significantly more favourable microbiological outcome when compared with patients in the control group.

I) Clearance of the initial organism with no detectable bacterial growth was statistically significant in the study group compared to the control group (80% vs. 52%, \( P = 0.03 \)).

II) Clearance of the initial organism but with emergence of a new organism (4% vs. 8%, \( P =1.0 \)) in study vs. control groups respectively.

III) Clearance of one of the initial causative organisms but with persistence of the other initial organism in multiple bacterial infection (4% vs. 4%, \( P =1.0 \)) in study vs. control groups respectively.

IV) Persistence of the initial causative organism (8% vs. 20%, \( P =0.42 \)) in study vs. control groups respectively.

V) Persistence of the initial organism in addition to emergence of a new organism (4% vs. 16%, \( P =0.35 \)) in study vs. control groups respectively.

VI) Clearance of the initial MDR organism was remarkably significant in the study group compared to the control group [7/7 (100%) vs. 4/11 (36%), \( P =0.01 \)].

Table (4): Microbiological outcome after 5 days of treatment in study and control groups.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study (n=25)</th>
<th>Control (n=25)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I) Clearance</td>
<td>20 (80%)</td>
<td>13 (52%)</td>
<td>0.03</td>
</tr>
<tr>
<td>II) Clearance of the causative organism &amp; Emergence of a new organism</td>
<td>1 (4%)</td>
<td>2 (8%)</td>
<td>1.0</td>
</tr>
<tr>
<td>III) Clearance of one organism &amp; Persistence of the other in multiple bacterial infection</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>1.0</td>
</tr>
<tr>
<td>IV) Persistence of the causative organism</td>
<td>2 (8%)</td>
<td>5 (20%)</td>
<td>0.42</td>
</tr>
<tr>
<td>V) Persistence of the causative organism &amp; Emergence of a new one</td>
<td>1 (4%)</td>
<td>4 (16%)</td>
<td>0.35</td>
</tr>
</tbody>
</table>
mechanically ventilated patients
the second most common nosocomial infection
risk early in the course of hospitalization
mechanically ventilated patients, with the highest
5) Safety of treatment:
- No renal Impairment was detected in study
group (0%) vs. (8%) in control group with no
significant difference between both groups
($P=0.49$).
- No adverse effects related to inhaled colistin
(neurotoxicity, bronchoconstriction, cough,
apnea or chest tightness) were recorded.

**DISCUSSION**

VAP is estimated to occur in 9-27% of all
mechanically ventilated patients, with the highest
risk early in the course of hospitalization $^{[14]}$. It is the
second most common nosocomial infection
in the ICU and the most common in mechanically ventilated patients $^{[17&18]}$. Mortality
rates in patients with VAP range from 20 to 50%
and may reach more than 70% when the
infection is caused by MDR and invasive pathogens $^{[14&19]}$. Recent years have witnessed a
steady increase in the proportion of VAP cases
caused by MDR Gram-negative bacteria
Acinetobacter baumannii, Pseudomonas aeruginosa, and Klebsiella pneumoniae in particular.
Some studies have shown that sputum and lung tissue antibiotic levels achieved after
inhalation are higher than those obtained after IV administration $^{[20]}$. Aerosolized colistin might be
an alternative suitable option for treatment of patients with VAP, because it achieves higher
pulmonary concentrations with ignorable
systemic absorption and toxicity, and without
increasing the risk of emergence of MDR gut microflora $^{[21]}$. The present study included 50
patients with a confirmed diagnosis of Gram-negative VAP who were randomly assigned into
two equal groups; a study group and a control
group. The study group received the
conventional systemic IV antibiotic regimen plus
adjunctive inhaled colistin (CMS) regimen via jet
nebulizer: 1 million IU of CMS every 8 hours, a
total 3 million IU /day, for a period of 5 days.
The control group received the conventional
systemic IV antibiotic regimen alone.
In the present study, most of the patients
were men (76%). The study group included 25
patients mean age (52.4± 17.2) years, 76% males
and 24% females. The control group included 25
patients mean age (53.6± 18.6) years, 76% males
and 24% females. There was no statistically
significant difference between both groups
regarding age and sex.
A similar study, a randomized controlled
trial on VAP patients which included two
groups; a study group (received IV antibiotics
plus nebulized CMS) and a control group
(received IV antibiotics plus nebulized sterile
saline). The study group mean age was
(70.2±18.5) years and included 60.8% males and
39.2% females. The control group mean age was
(66.2±15.8) years and included 67.3% males and
32.7% females. There was no statistically
significant difference between both groups
regarding age and sex $^{[22]}$.
The underlying co-morbidities that indicated
mechanical ventilation and ICU admission in the
present study, were neurological causes and head
trauma in [(56% vs. 60%) 58% of total patients],
respiratory causes [(28% vs. 40%) 34% of total
patients], hepatic causes [(12% vs. 0%) 6% of
total patients] and cardiac causes [(4% vs. 0%)
2% of total patients] in study vs. control groups
respectively. There was no statistically
significant difference between both groups
regarding underlying co-morbidities.
A clinical study on VAP patients in the ICU
showed that the indications for mechanical
ventilation were neurological and head trauma
(62%), respiratory failure (10%), suicidal
poisoning (7%) and others (21%) $^{[23]}$. The
present study showed that the initial
causative organisms were: Klebsiella spp. [(48% vs.
16%) representing 32% among total patients],
Acinetobacter spp. [(20% vs. 32%) representing
26% among total patients], Pseudomonas spp.
[(12% vs. 36%) representing 24% among total
patients], Multiple growth (Klebsiella &
Pseudomonas) [(12% vs. 4%) representing 8%
among total patients], Multiple growth
(Klebsiella & Acinetobacter) [(4% vs. 4%)
representing 4% among total patients], E.Coli
[(4% vs. 0%) representing 2% among total
patients] and Citrobacter spp. [(0% vs. 4%)
representing 2% among total patients], Proteus
spp. [(0% vs. 4% representing 2% among total
patients) in study vs. control groups respectively.
There was no statistically significant difference
between both groups regarding the initial
causative organisms except for Klebsiella spp.
($P=0.01$) which was the major causative
organism of VAP in this study.
In contrast, a retrospective study on VAP
patients showed that the initial causative
organisms in aerosolized (AS)-IV colistin group
vs. IV colistin group respectively were
Acinetobacter spp. [69.2% vs. 53.8%]
representing 61.5% among total patients],
Pseudomonas spp. [23.1% vs. 26.9%]
representing 25% among total patients] and
Klebsiella spp. [7.7% vs. 19.2%]
representing 13.5% among total patients]. There was
statistically significant difference between both
groups as regarding Acinetobacter spp. ($P=0.02$)
which was the major causative organism of VAP
in their study $^{[24]}$. 

28
In the present study, patients in the study group had significantly more favourable microbiological outcome when compared with patients in the control group. Clearance of the initial causative organism with no detectable bacterial growth was statistically significant (80% vs. 52%) in the study vs. control groups respectively \((P=0.03)\). Clearance of the initial MDR organisms were remarkably significant in study vs. control groups respectively (100% vs. 36%, \(P=0.01)\).

A randomized controlled trial was conducted to evaluate the efficacy and safety of nebulized CMS as adjunctive therapy in patients with Gram-negative VAP using a dose 2.25 million IU/12 hrs for 28 days. They noted that favorable microbiological outcome was significantly higher in the patients who received nebulized CMS when compared with the control group (60.9% vs. 38.2%, \(P=0.03)\). This study was different from our study in the dose and duration of colistin inhalation. Furthermore, they considered a favorable microbiological outcome even if it was just a presumed eradication without a documented culture result. Our study considered clearance of the organism only with a documented culture results. Another study used high dose 5 million IU every 8 h of nebulized colistin, 15 million IU/day, for an average duration 12 days in patients with VAP caused by MDR organisms via a vibrating plate nebulizer monotherapy alone without adjunctive systemic IV antibiotics. They finally concluded that nebulized colistin at high dose is effective and safe for treating VAP caused by MDR \(P. aeruginosa\) and \(A. baumannii\).

Regarding safety of treatment in the present study; No renal Impairment was detected in the study group (0%) vs. (8%) in the control group with no significant difference between both groups. No adverse effects related to inhaled colistin were detected (neurotoxicity, bronchoconstriction, cough, apnea or chest tightness).

A systematic review and meta-regression analysis for the efficacy and safety of aerosolized colistin in VAP patients. The overall reported nephrotoxicity did not differ significantly between group received colistin and control group. Also, neurotoxicity did not differ significantly between both groups.

A systematic review and meta-analysis done by using aerosolized colistin for the treatment of MDR VAP, showed that there was no significant difference in nephrotoxicity between group received colistin and control group.

REFERENCES


