Original Article

Effect of extended infusion of meropenem and nebulized amikacin on Gram-negative multidrug-resistant ventilator-associated pneumonia

ABSTRACT

Background: Ventilator-associated pneumonia (VAP) due to multidrug-resistant organisms (MDROs) is associated with a significant mortality in the Intensive Care Unit (ICU). The aim of this study was to compare the efficacy and safety of extended infusion of meropenem and nebulized amikacin on VAP caused by Gram-negative MDRO versus intravenous (IV) meropenem and amikacin alone.

Methodology: A randomized nonblinded controlled trial was performed on ninety patients with VAP. Patients were randomized into three equal groups: Group I received IV amikacin 20 mg/kg/24 h and meropenem 2 g over 30 min/8 h. Group II received the same as Group I in addition to nebulized amikacin 25 mg/kg/day every 8 h. Group III received IV amikacin 20 mg/kg/24 h, nebulized amikacin 25 mg/kg/day every 8 h, and meropenem 2 g diluted in 240 ml normal saline over 3 h/8 h. The primary outcome was the clinical outcome of VAP. Secondary outcomes were microbiological outcome, VAP-related mortality, duration of MV, ICU stay, and nephrotoxicity.

Results: Group II and Group III compared to Group I showed higher incidence of clinical cure (53.33% in Group II and 66.67% in Group III vs. 26.67% in Group I, $P = 0.007$). Group II compared to Group I showed significant reduction in ventilator days (5.32 ± 1.86 vs. 7.3 ± 2.1 days, respectively, $P < 0.001$) and reduction in ICU days (11.87 ± 2.6 vs. 15.3 ± 3.1 days, respectively, $P < 0.001$). Group III compared to Group II showed significant reduction in ventilator days (4.22 ± 1.32 vs. 5.32 ± 1.86, respectively, $P = 0.011$) and highly significant reduction in ICU days (9.21 ± 1.17 vs. 11.87 ± 2.6, respectively, $P < 0.001$). All groups were comparable as regards nephrotoxicity or mortality.

Conclusions: Adding nebulized amikacin to systemic antibiotics in patients with VAP caused by Gram-negative MDRO may offer efficacy benefits, and the use of extended infusions of meropenem could improve the clinical outcomes in critically ill populations.

Key words: Amikacin; extended infusion; meropenem; nebulized; ventilator-associated pneumonia

Introduction

Ventilator-associated pneumonia (VAP) is defined as an infection of the lower respiratory tract associated with endotracheal intubation and causes significant morbidity and mortality in the Intensive Care Unit (ICU). It is considered to be one of the most common health care-associated infections arising in the ICU.[1] About 10% of ventilated

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patients will develop the disease, with the risk of VAP rising as the durations of mechanical ventilation increase, reaching a maximum on day 5 postintubation.[2] Further, VAP is associated with a significant morbidity as it increases the length of stay in the ICU, duration of mechanical ventilation, and hospital stay.[3]

VAP caused by multidrug-resistant organisms (MDROs) is associated with much more mortality.[4,5] Potential MDROs include *Acinetobacter* spp., *Klebsiella*-producing carbapenemase strains, ESBL-producing *Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, and methicillin-resistant *Staphylococcus aureus*. Diagnosing VAP requires combined assessment of clinical data, microbiological results, and radiological findings. There are no simple and easy methods to determine that a patient has VAP. When there is a high clinical suspicion of VAP, empirical therapy with antimicrobial must be started immediately because both delayed management and inadequate treatment are associated with an increased incidence of morbidity and mortality.[6] Recommendations of the current guidelines include coverage of Gram-negative bacilli (GNB) empirically with a carbapenem, piperacillin-tazobactam, and a third- or fourth-generation cephalosporin, in combination with an aminoglycoside or a fluoroquinolone.[7] However, there will be a problem when a high proportion of the GNB are not sensitive to these antibiotics. One of the sequelae of a greater prevalence of resistance to antimicrobials is an increased realization of inadequate treatment of infection. Alternatives available for the treatment of Gram-negative multidrug-resistant (MDR) bacilli are few.

The administration of inhaled antibiotics offers the possibility of providing high drug levels in the lung tissue and reduction of the systemic toxicity that occur with intravenous (IV) antibiotics. The concentration of the inhaled antibiotics in the respiratory secretion may be 20 to 100 folds higher than *in vitro* minimum inhibitory concentration (MIC) of the organisms being treated.[8]

An increased resistance to antimicrobials and the shortage of new antimicrobial development necessitate new dosing strategies to optimize the pharmacodynamics of the existing antimicrobials. This can aid in preserving antibiotic efficacy, impede the emergence of resistance, and provide a pharmaco-economic benefit. Meropenem and piperacillin-tazobactam both exhibit time-dependent killing and are used in the treatment of infections caused by MDR bacteria. Prolonged infusions of these antimicrobials increase the time of exposure above the MIC and should as a result improve their efficacy.[9]

Methodology

This study was a prospective, randomized, nonblinded, controlled, single-center trial performed at the ICU of Ain Shams University Hospitals, a 42-bed medical-surgical ICU, from October 2015 to December 2016.

Patients requiring mechanical ventilation were candidates for the study if they met the following inclusion criteria: 18 years old or greater and patients having ventilator-associated pneumonia (VAP) with positive sputum culture showing Gram-negative MDRO. VAP was considered if the onset occurred following intubation of the trachea for 48 h and the infection was absent before starting mechanical ventilation.[7]

Diagnosis of pneumonia was based on radiographic finding of pulmonary infiltrate; findings should be new and progressive and at least should satisfy two clinical criteria of the following: body temperature >38°C or <35.5°C; leukocyte count >12,000 cells/mm^3 or <4000 cells/mm^3; and clinical evidence of pneumonia, such as purulent secretions and a decrease in oxygenation.

Diagnosis of VAP was confirmed microbiologically by positive bronchial secretion cultures.[10] Exclusion criteria included pregnancy, use of immunosuppressive agents except for steroids, neutropenia (white blood cell count ≤1000/mL), history of allergy to the study drugs, patients whose primary diagnosis was community-acquired pneumonia, or patients with renal impairment necessitating dose adjustment of any of the study drugs.

After obtaining approval from Ain Shams University Hospital's Ethical Committee and obtaining informed consent from patients' first-degree relatives, ninety patients were randomized into three groups. Patient recruitment, enrollment, and analysis were depicted in Figure 1. Randomization was performed using a sealed envelope design. Envelopes containing the information of the randomization were sealed and kept in the folder of patients until the end of the study.

Group I (control group): received amikacin 20 mg/kg diluted in 100 ml normal saline (NS) to be given over 1 h/24 h and meropenem 2 g diluted in 100 ml NS over 30 min/8 h.

Group II (nebulized AB group): received amikacin 20 mg/kg diluted in 100 ml NS to be given over 1 h/24 h, meropenem 2 g diluted in 100 ml over 30 min/8 h, and amikacin 25 mg/kg/day to be divided every 8 h and diluted in 4 ml NS nebulized by an ultrasound nebulizer.

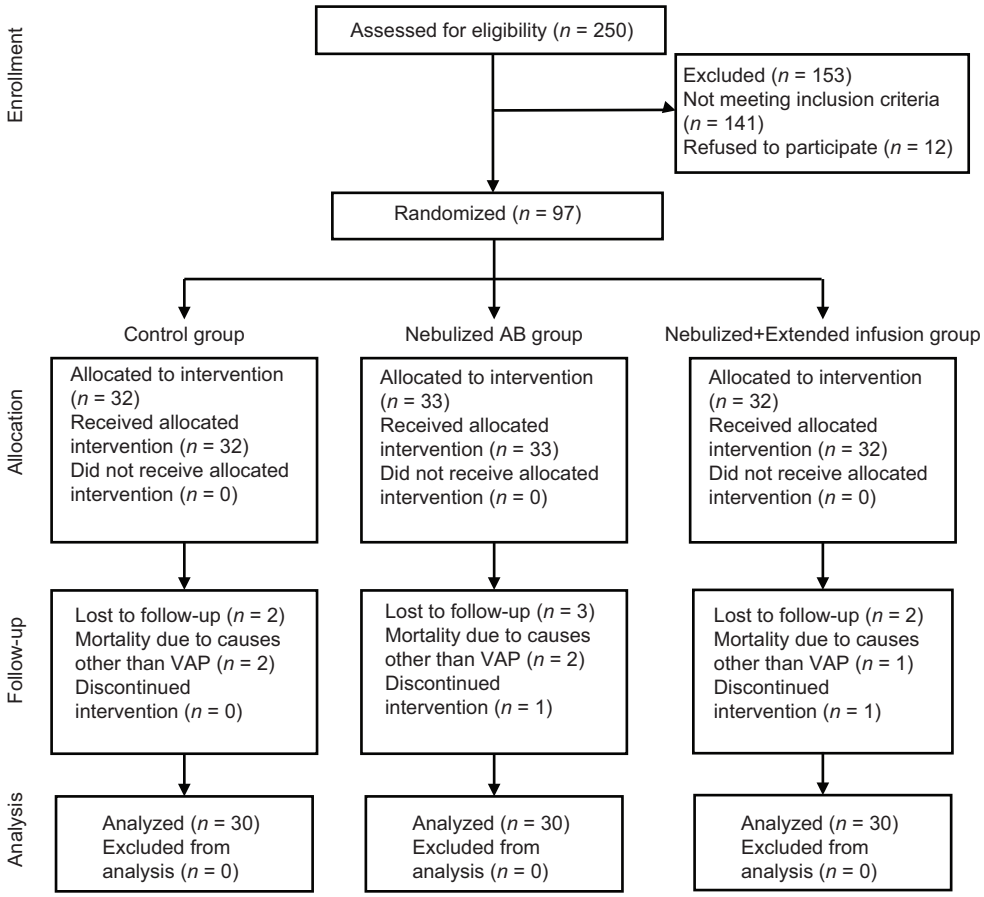

Figure 1: Flowchart for patient recruitment, enrollment, and analysis

Group III (nebulized AB + extended infusion group): received amikacin 20 mg/kg diluted in 100 ml NS to be given over 1 h/24 h, amikacin 25 mg/kg/day to be divided every 8 h and diluted in 4 ml NS nebulized by an ultrasound nebulizer, and meropenem 2 g diluted in 240 ml NS over 3 h/8 h.

The primary outcome of the study was the clinical outcome of VAP. Clinical outcome was classified as: clinical cure (i.e., resolution of infection symptoms and signs by the end of antibiotic treatment) and clinical improvement (i.e., partial resolution of infection symptoms and signs). Clinical cure or clinical improvement was considered as the clinical success. As secondary outcomes, VAP-related mortality, microbiological outcome, duration of mechanical ventilation, ICU stay, and the incidence of adverse events during treatment were evaluated.

The Acute Physiology and Chronic Health Evaluation score at the time of randomization defined as clinical severity of illness, Clinical Pulmonary Infection Score (CPIS), and adverse events were monitored on a daily basis.

Microbiological outcome was categorized as eradication of the pathogen (i.e., no growth in the final culture during hospitalization) and persistence of pathogen (i.e., persistent growth of the pathogen regardless of the clinical outcome).

The definition of VAP-related mortality was considered if death occurred during the treatment period due to septic shock and signs of pneumonia remained.

Nephrotoxicity was defined as a value of serum creatinine >2 mg/dL; as a decline in creatinine clearance of 50%, in comparison to the baseline value; or as a reduction in renal function that necessitated renal replacement therapy.

Adverse effects related to nebulized amikacin use, such as cough, bronchoconstriction, chest tightness or apnea, and arterial hypoxemia, were recorded.

Nebulization technique

Nebulization was performed with an ultrasound nebulizer positioned on the inspiratory limb proximal to the Y-piece. To reduce flow turbulences and extrapulmonary deposition, specific ventilator settings were used during the nebulization period. They included removal of the humidifier (heat and moisture exchanger), volume-controlled mode, constant inspiratory flow, respiratory rate of 12 breaths/min,

inspiratory: expiratory ratio of 1–2, tidal volume of 8 ml/kg, and an end-inspiratory pause representing 20% of the duty cycle. Synchrony between the patient and the ventilator was guaranteed by deepening the level of sedation to avoid inspiratory turbulences and optimize distal lung deposition of nebulized particles.

Statistical analysis

Before the study, a power analysis was performed to determine the minimal acceptable number of patients in each group on the basis of the expected clinical outcome. The minimal sample number was 27 participants for each group with type I α-error of 0.05 and type II β-error of 0.1, with the power of the test at 90%; so, we set the group number at 30 for compensation of any possible dropouts.

Data were collected, revised, coded, and entered into the Statistical Package for Social Sciences (SPSS) version 20 computer software (IBM Corp. 2011. IBM SPSS Statistics for Windows, Version 20.0, IBM Corp., Armonk, NY, USA). The qualitative data were presented as number and percentages while quantitative data were presented as mean, standard deviations, and ranges, when their distribution was found parametric. The comparisons between two groups with qualitative data were done using Chi-square test. The comparison between more than two independent groups with quantitative data and parametric distribution was done using one-way analysis of variance followed by *post hoc* analysis using Fisher's least significant difference test. The confidence interval was set to 95% and the margin of error accepted was set to 5%. Hence, the *P* value was considered statistically significant at $P < 0.05$.

Results

All groups were comparable with regard to age, sex, cause of ICU admission, and APACHE II score [Table 1].

Adding nebulized amikacin to systemic antibiotics in VAP caused by MDRO (Group II), compared with systemic antibiotics only (Group I) resulted in a significant reduction in ventilator days (5.32 ± 1.86 vs. 7.3 ± 2.1 days, respectively, $P < 0.001$) and reduction in ICU days (11.87 ± 2.6 vs. 15.3 ± 3.1 days, respectively, $P < 0.001$). Changing the method of administration of meropenem to extended infusion (Group III compared to Group II) resulted in significant reduction in ventilator days (4.22 ± 1.32 vs. 5.32 ± 1.86, respectively, $P = 0.011$) and highly significant reduction in days of stay in ICU (9.21 ± 1.17 vs. 11.87 ± 2.6, respectively, $P < 0.001$). There was no difference in VAP-related mortality and nephrotoxicity between groups. At the end of treatment, CPIS was lower in Group III than Group II which was less than Group I with high statistically significant difference (3.6 ± 0.2 vs. 4.2 ± 0.7 vs. 5.3 ± 0.4, respectively, $P < 0.001$) [Table 2].

At the end of therapy, nebulized AB group (Group II) and nebulized + extended infusion AB group (Group III) compared to control group (Group I) showed higher incidence of clinical cure (53.33% patients in Group II and 66.67% patients in Group III vs. 26.67% patients in Group I; $P = 0.007$); the results were statistically significant. There was no difference between groups in clinical improvement.

Microbiological response, either bacterial persistence or bacterial eradication, was comparable among groups with no statistical significance [Table 3].

Table 1: Baseline clinical characteristics of patients

Characteristics	Group I ($n=30$)	Group II ($n=30$)	Group III ($n=30$)	One-Way ANOVA	
				F	*P*
Age					
Mean±SD	54.85±4.33	55.5±3.85	55.8±3.47	0.465	0.629
Range	50-60	51.5-60	50.5-60		
Sex (%)					
Males	21 (70.0)	23 (76.67)	24 (80.0)	0.842	0.656
Females	9 (30.0)	7 (23.33)	6 (20.0)		
Cause of ICU admission (%)					
Trauma	13 (43.33)	12 (40.0)	11 (36.67)	1.767	0.778
Surgical	9 (30.00)	12 (40.0)	9 (30.0)		
Medical	8 (26.67)	6 (20.0)	10 (33.33)		
CPIS starting treatment					
Mean±SD	8.3±0.85	8.65±0.67	8.43±0.86	1.474	0.235
APACHE II					
Mean±SD	18.7±2.0	20.0±3.0	19±2.0	2.453	0.092

$P<0.05$; statistically significant difference. Data are presented as mean±SD or *n* (%). ANOVA: Analysis of variance; ICU: Intensive Care Unit; CPIS: Clinical Pulmonary Infection Score; APACHE: Acute Physiology and Chronic Health Evaluation; SD: Standard deviation

Table 2: Treatment efficiency, mortality, and adverse events

Variable	Group I (n=30)	Group II (n=30)	Group III (n=30)	One-Way ANOVA		P 1	P 2	P 3
				F	P			
CPIS after treatment								
Mean±SD	5.3±0.4	4.2±0.7	3.6±0.2	9.957	<0.001	<0.001	<0.001	<0.001
Ventilator days (after inclusion)								
Mean±SD	7.3±2.1	5.32±1.86	4.22±1.32	22.810	<0.001	<0.001	<0.001	0.011
Length of ICU stay after inclusion (days)								
Mean±SD	15.3±3.1	11.87±2.6	9.21±1.17	47.293	<0.001	<0.001	<0.001	<0.001
VAP-related mortality (%)	8 (26.67)	5 (16.67)	4 (13.33)	1.886	0.389	0.347	0.197	0.717
Nephrotoxicity (%)	4 (13.33)	3 (10.0)	4 (13.33)	0.207	0.902	0.687	1.000	0.687

Data are presented as mean±SD or n (%). P<0.05, statistically significant difference. ANOVA: Analysis of variance; CPIS: Clinical Pulmonary Infection Score; ICU: Intensive Care Unit; VAP: Ventilator-associated pneumonia; SD: Standard deviation

Table 3: Clinical and microbiological responses

Variable	Group I (n=30)	Group II (n=30)	Group III (n=30)	Chi-square test		P 1	P 2	P 3
				χ^2	P			
Clinical cure (%)	8 (26.67)	16 (53.33)	20 (66.67)	9.960	0.007	0.035	0.002	0.292
Clinical improvement (%)	6 (20.0)	7 (23.3)	8 (26.67)	0.373	0.831	0.754	0.541	0.765
Bacterial persistence (%)	9 (30.0)	10 (33.33)	11 (36.7)	0.300	0.861	0.781	0.583	0.787
Bacterial eradication (%)	10 (33.3)	9 (30.0)	11 (36.67)	0.300	0.861	0.781	0.787	0.583

Data are presented as n (%). P<0.05, statistically significant difference

No adverse effects related to nebulized amikacin were recorded.

Discussion

Inhaled antibiotics for VAP caused by organisms that are MDR were recommended by the American Thoracic Society guidelines from 2005 only when IV antibiotics have failed.[7] Since those guidelines were written, there have been many trials using these agents as primary therapy or as adjuncts to treat VAP caused by MDR organisms.

The findings of the present study were that VAP treatment with nebulized amikacin was associated with higher rates of clinical cure, improved CPIS score, and less ventilator and ICU days when used as adjunctive therapies for the treatment of VAP caused by MDR Gram-negative bacteria. There was no difference in VAP-related mortality and nephrotoxicity between groups. Microbiological response was comparable among groups.

Lu *et al*.[11] reported that results of nebulized ceftazidime and amikacin were similar in terms of successful treatment, treatment failure, and superinfection with other microorganisms with the same antibiotics when administered through the IV route in patients with VAP due to *P. aeruginosa*.

These findings are noteworthy because the study group received nebulized antibiotics alone without IV therapy.

Arnold *et al*.[12] reported that adjunctive use of nebulized antibiotics was associated with improvement of survival in a retrospective, cohort, single-center study of patients with VAP caused by *Acinetobacter baumannii* or *P. aeruginosa*.

Palmer and Smaldone[13] concluded that the use of inhaled antibiotics led to the eradication of resistant organisms in tracheal secretions and reduced the incidence of new resistance to systemic agents. No resistance to the inhaled drug emerged. CPIS improved significantly in aerosolized AB compared with placebo.

In this study, we used extended infusion strategy; a significant improvement in outcomes was demonstrated as regards reduction in ventilator days and ICU length of stay, lower CPIS score, as well as decrease in the incidence of mortality.

Nicasio *et al*.[14] in a prospective, observational study with a historical (retrospective) control group presented reduced VAP-related mortality, length of stay, and fewer events of superinfection in patients treated by administration of extended infusions of cefepime 2 g over 3-h every 8 h or 2 g meropenem every 8 h in addition to tobramycin and vancomycin. The retrospective control design of these studies strongly affects their power.

In a study by Dow *et al*.,[15] a total of 121 patients were included: 67 patients in the prolonged infusion group (81% piperacillin-tazobactam and 19% meropenem) and

54 patients in the intermittent (67% piperacillin-tazobactam and 33% meropenem) group.

The prolonged infusion group showed a significant decrease in ventilator days, ICU length of stay, and hospital length of stay compared with the intermittent group. The risk of in-hospital mortality was 12.4% in the prolonged infusion group and 20.7% in the intermittent group.

Limitations of the study

This was a single-center study, and the treating intensivists were not blinded to the arms of the study.

Conclusions

The use of nebulized amikacin as an adjunctive therapy in patients with VAP caused by MDR Gram-negative organisms may offer efficacious benefits over systemic antibiotics alone, and the use of extended infusions of meropenem could add an improvement in the clinical outcomes in critically ill populations. As there is an increase in antibiotic resistance in Gram-negative organisms, these dosing strategies and method of administration will be important for appropriate treatment.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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