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Management of ventilator-associated pneumonia: A comparison of two therapeutic approaches due to multidrug-resistance *Acinetobacter*; a controlled clinical trial study

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Abstract

Introduction: Ventilator-associated pneumonia (VAP) is a complicated condition that usually occurs two-three days after endo-tracheal intubation and is characterized by some signs and symptoms such as fever, changed white blood cell count and chest infiltration.
Objectives: Our study was aimed at comparing the therapeutic effects of meropenem, injectable colistin plus nebulized colistin and meropenem, injectable colistin, plus nebulized G-CSF (granulocyte-colony stimulating factor) in patients with VAP as a result of multidrug-resistance Acinetobacter.
Patients and Methods: VAP patients were randomly divided into two groups (n= 30/each; control group are patients who received IV (intravenous) meropenem, injectable colistin plus nebulized colistin, as a routine treatment, while the intervention group consisted of patients who received IV meropenem, injectable colistin, plus nebulized G-CSF. A total of 14 days of therapeutic intervention are required for every case. Follow-up for subjects was performed at 5 time-points; days 1, 3, 5, 7, and 14 after intervention. In the present study, the clinical pulmonary infection score (CPIS) was determined on the basis of points assigned for various clinically manifestations of VAP.
Results: The mean of ages in the two groups of routine treatment and intervention were 60.1 ± 13.7 years and 59.7 ± 18.4 years, respectively. There is no significant difference between ages in two groups of subjects ($P=0.93$). Based on our statistically analysis, no significant difference between CPIS in both groups 1 and 2 was detected ($P>0.05$).
Conclusion: CPIS and some other clinical investigations appeared effectiveness of the treatment with injected colistin, nebulized colistin plus nebulized G-CSF for management of VAP. Based on the results of our study, aforementioned therapeutic approach can be used as an alternative treatment for the management of infection in VAP cases; however, in order to make a definite statement about the effectiveness of our proposed treatment, further studies with a cellular and molecular approach are necessary.
Trial Registration: This study was registered at the Iranian website for registration of clinical trials (#IRCT20150824023743N2, https://irct.ir/trial/41023, with regional ethical code of IR.MUI.MED.REC.1397.052).

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Introduction

Ventilator-associated pneumonia (VAP) is a complicated condition that usually occurs two-three days after endo-tracheal intubation and is characterized by some signs and symptoms such as fever, changed white blood cell count and chest infiltration (1-3). Aforementioned condition contributes to nearly 50% of all acquired pneumonia patients in hospital (3). VAP is one of the most common hospitalized nosocomial infections especially in patients that received mechanically ventilator in the intensive care units (ICUs) (4, 5). Despite increasing advances in medical and health sciences to reduce the risk of infection transmission in ICUs, infection control in VAP patients is still a major challenge for infectious disease specialists. High mortality rate has been reported in VAP, especially in cases that its occurrence is associated with high-risk pathogens (6). As it is known, proper anti-microbial therapy significantly

Key point

Current trial was designed to examining the therapeutic effects of meropenem, colistin, versus nebulized colistin (as a routine approach) and meropenem, colistin, and nebulized granulocyte-colony stimulating factor (as a novel approach) in cases with ventilator associated pneumonia as a result of multidrug-resistance *Acinetobacter*. Our results appeared effectiveness of the treatment with injected colistin, nebulized colistin plus nebulized granulocyte-colony stimulating factor for management of ventilator associated pneumonia.

increases the optimistic consequence of the management. Furthermore, rapid documentation of patients and choice of a suitable therapeutic approach plays a critical role in controlling infection in VAP cases (7,8). The types of micro-organism that triggered respiratory system play a crucial role in predicting therapeutic success in VAP patients. Previously reported that the rate of mortality as result of *Acinetobacter* or *Pseudomonas pneumonia*, pulmonary infection with the gram-negative pathogen *P. aeruginosa* in VAP cases, was 87% compared with 55% for pneumonias triggered with other pathogens (9). Multi-drug resistance (MDR) *Acintobacter* plays a key and considerable role in the occurrence of VAP. Descriptions of MDR *Acinetobacter* types vary when referring to a wide array of phenotypes and genotypes. MDR *Acinetobacter* has been defined as the resistant to at least three classes of antimicrobial drugs—all penicillins and cephalosporins, fluroquinolones, and aminoglycosides.

As previously mentioned, pneumonia is responsible for a remarkable mortality rate worldwide. It has been suggested that granulocyte-colony stimulating factor (G-CSF) plays an important role for management of pneumonia in adults (10). G-CSF is one of the more important glycoproteins that plays a crucial role in stimulation of progenitor cells in the bone marrow to release granulocytes into blood (11,12). Furthermore, it has been proposed that G-CSF increases stimulation of neutrophil precursors and this is useful in reducing the duration of febrile neutropenia (13). Administration of G-CSF for the management of infections is based on some facts such as increase uptake of antibiotics, immune-modulation of the cytokine response, and enhanced chemotaxis (14,15).

Objectives

The current trial was designed to examining the therapeutic effects of meropenem, colistin, and nebulized colistin (as a routine approach) and meropenem, colistin, and nebulized G-CSF (as a novel approach) in cases with VAP as a result of multidrug-resistance *Acinetobacter*.

Patients and Methods

Patients

Current randomized clinical trial was accepted by the infectious diseases department of School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. The main purpose of our clinical trial study was to compare the therapeutic effects of injectable colistin plus nebulized colistin and injectable colistin plus nebulized G-CSF in VAP cases at two weeks of follow-up. Moreover, we surveyed some other clinical presentations of volunteers.

Furthermore, demographic data of each case was documented in separated forms. Inclusion criteria were mechanical ventilation for more than 48 hours, precise diagnosis of VAP that generated by multidrug resistance *Acinetobacter,* and age more than18 years. Exclusion criteria were age less than 18 years, consumption of immunosuppressive drugs, pregnancy and allergy to colistin, occurrence of catheter-associated infection, infections of urinary system, and other infection conditions. Our criteria for diagnosis of VAP were purulent bronchial secretions, appearance of chest infiltration on radiographs, leukocyte count >11.103/μL, body temperature >38.4°C or <36.5°C. Lower respiratory tract sampling was done by fiberoptic bronchoscopy then *Acinetobacter* was settled. Presence of at least 10^4 colony forming units/mL was considered for precise diagnosis of VAP that triggered by *Acinetobacter*. VAP cases were distributed into control and intervention (n=30/each).

In the control group, individuals received meropenem intravenously (Loghman, Iran) (2 g/8 h for 2 weeks), nebulized colistin (with a dose of 9 million IU and then 4.5 million IU every 12 hours for 2 weeks) plus injectable colistin (UK company), as a routine treatment while in the intervention group, individuals received IV (intravenous) meropenem (2 g/8 h for 2 weeks), colistin plus nebulized G-CSF (Arya TinaGen) with the dose of 150 μg every 48 hours for two weeks.

Follow-up procedure

A total of two weeks of intervention was required for every subject included in our study. Follow-up for patients was executed at days 1, 3, 5, 7, and 14 after intervention. In the current trial, we calculated the clinical pulmonary infection score (CPIS) according to the protocol reported by Zilberberg et al (16). At each visit by the infectious disease specialist, cases will be assessed for possible changes in clinical status. On day 14, the state of the patients and the pathology results of respiratory discharge were recorded.

Statistical analysis

Data were analyzed by of SPSS version 22.0 (SPSS Inc, USA) and some statistic tests such as independent *t* test and chi-square test. *P* value less than 0.05 was considered as meaningful difference.

Results

In the current trial study, volunteers (n=60) were divided into the two groups of case and control (Figure 1). The mean ages in the two groups of control and case were 60.1 ± 13.7 years and 59.7 ± 18.4 years of old, respectively. There is no considerable alteration between ages in two

groups ($P=0.93$). Some of the substantial demographic data and characteristics of the volunteer are summarized in Table 1.

Table 2 highlights the results of presence or absence of co-morbidities. There was no significant difference between CPIS scores ($P>0.05$). Table 3 shows the outcomes of CPIS scores (five times).

Discussion

VAP is stated to be one of the leading causes of death in ICU patients. Attention to various aspects of VAP therapy has been considered by pharmaceutical researchers for many years. Recently, the therapeutic aspects of G-CSF for management of respiratory complications have been considered. It has been proposed that this factor serves as a crucial agent for respiratory system homeostasis and protection from pathogens(10). Steinwede et al in their experimental study investigated the effects of G-CSF on Pneumococcal pneumonia in mice (17). They concluded that GM-CSF stimulates the immunity reaction in the animal's lung and protect mice from lethal pneumococcal pneumonia by means of improving antibacterial immunity. They proposed that the aforementioned agent protects immune-compromised subjects against bacterial pneumonia. In another study, Unkel et al reported that cellular cross talk between influenza virus- infected alveolar epithelial cell (AECs) and anti-viral immune response, is important for effective viral clearance and protect the respiratory system from injury (18), they reported the considerable role of G-CSF in above successful cross talk. Standiford et al reported that toll-like receptor4 (TLR4) dependent GM-CSF protects against lung injury in gram-negative bacterial pneumonia. They also presented that GM-CSF protects AECs from bacterial associated injury (19). In the present study, management of VAP patients with new therapeutic approach, IV meropenem, injectable colistin), nebulized colistin plus nebulized G-CSF improved the patient's status.

One of main limitations was a few numbers of patients that participated in the current randomized clinical trial. What is certain is that many more patients are needed to comment on the effectiveness of a new treatment. In current trial, accurate information on the history of use of various antibiotics as well as their resistance was not available and this accosts our results with the unsought bias. Furthermore, for examining the therapeutic effects of meropenem, injectable colistin, nebulized colistin plus nebulized G-CSF on management of patients with VAP, we used CPIS. Until now, some studies tried to assess the effectiveness of the CPIS for assessment of VAP patients. It has been accepted that a CPIS more than six may be related with presence of VAP. Papazian et al reported 85% specificity, 72% sensitivity, and 79% general reliability of CPIS (20). Above specificity, sensitivity, and reliability of CPIS related with restricted role assessment and diagnosis of VAP condition. Nevertheless, because of its repeatable

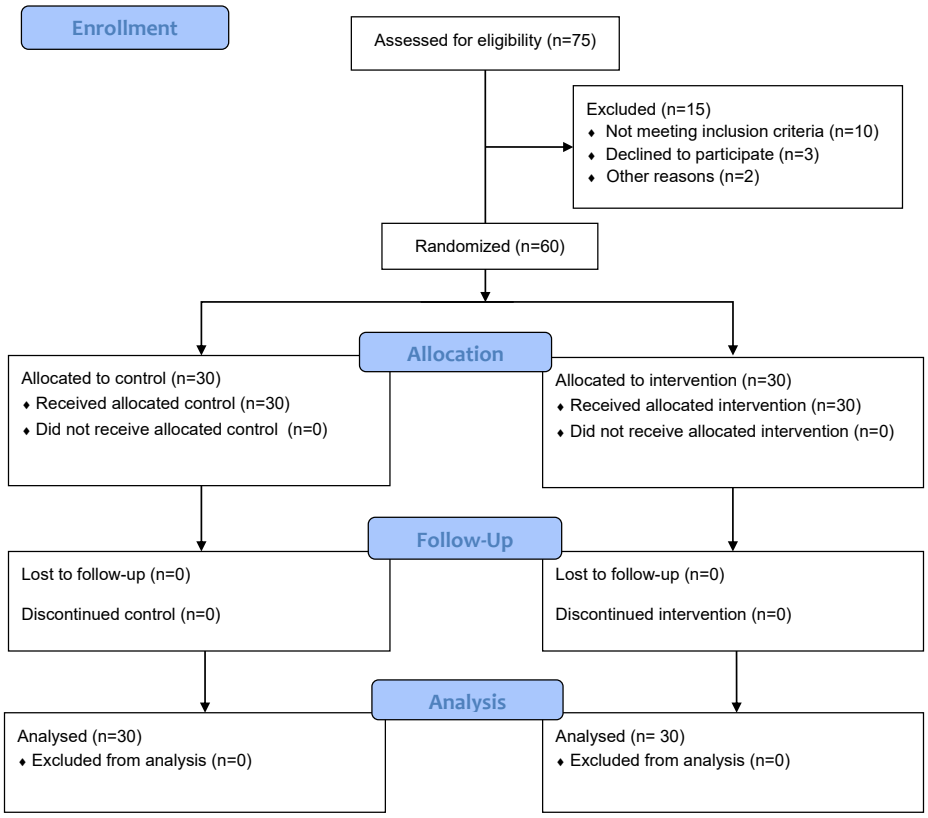

Figure 1. Flowchart of the study.

Table 1. Characteristics of the patients at the time of VAP suspicion

Characteristics	Intervention group (n = 30)	Routine treatment (n = 30)	*P* value
Age, years	59.7 ± 18.4	60.1 ± 13.7	0.93[a]
Gender [n. (%)]			0.59[b]
Female, n (%)	12 (40%)	10 (33.3%)	
Male, n (%)	18 (60%)	20 (66.7%)	
Hospital time (day)	13 ± 6.8	12.07 ± 5.6	0.56[a]
Ventilation time (day)	10.6 ± 6.2	11.3 ± 5.5	0.64[a]
Glasgow Coma Scale	5.53 ± 1	5.57 ± 1	0.9[a]
Decreased secretion	27 (90%)	28 (93.3%)	0.64[b]

[a] Independent *t* test, [b] Chi-square test.

Table 2. The results of our survey about co-morbidities of patients

	Intervention group (n = 30)	Routine treatment (n = 30)	P value
Comorbidities, n (%)			0.15
Cardiovascular disease	2 (6.7%)	1 (3.3%)	
Hypertension	5 (16.7%)	9 (30%)	
Diabetes	8 (26.7%)	5 (16.7 %)	
Chronic kidney disease	1 (3.3%)	0	
Lupus	0	1 (3.3%)	
Malignancy	4 (13.3%)	1 (3.3%)	
MS	1 (3.3%)	0	
Seizure	1 (3.3%)	0	
COPD	2 (6.7%)	0	
Wegener	1 (3.3%)	0	
Reason for mechanical ventilation, n (%)			0.62
Broncho-pneumonia	1 (3.3%)	0	
CVA	4 (13.3%)	6 (20%)	
SDH	2 (6.7%)	0	
Multiple trauma	1 (3.3%)	1 (3.3%)	
Sepsis	5 (16.7%)	4 (13.3%)	
Aspiration pneumonia	4 (13.3%)	3 (10%)	
COPD	1 (3.3%)	0	
SAH	5 (16.7%)	11 (36.7%)	
GIB	1 (3.3%)	0	
Uro-sepsis	1 (3.3%)	1 (3.3%)	
ICH	5 (16.7%)	4 (13.3%)	

Multiple sclerosis (MS), chronic obstructive pulmonary disease (COPD), cerebral vascular attack (CVA), subdural hematoma (SDH), subarachnoid hemorrhage (SAH), gastrointestinal bleeding (GIB), Intracerebral Hemorrhage (ICH).

Table 3. CPIS (mean ± SD) of the patients at the time of treatment

Characteristics	Intervention group (n = 30)	Routine treatment (n = 30)	*P* value
CPIS at start	9.07 ± 1.5	9.70 ±1.1	0.07
CPIS at 1st day	9.07 ± 1.5	9.4 ±1.3	0.37
CPIS at 3st day	6.7 ±1.8	6.9 ±1.6	0.76
CPIS at 5st day	4.1 ± 1.8	4.2 ± 1.5	0.81
CPIS at 7st day	2.4 ± 1.5	2.2 ± 1.01	0.69
CPIS at 14st day	1.1 ±0.9	1.1 ±0.5	1

CPIS, Clinical pulmonary infection score.
* Independent *t* test.

and non-invasive essence, it is widely used in clinical studies. In our trial, we did not see a considerabl alteration between the two groups of cases in terms of CPIS score. It means that meropenem, injectable colistin, nebulized colistin plus nebulized G-CSF can be considered as an alternative therapeutic approach for the management of infection in VAP cases.

Conclusion

According to CPIS, effectiveness of the treatment with injected colistin, nebulized colistin plus nebulized G-CSF for management of VAP was determined. Based on the results of our study, aforementioned therapeutic approach can be used as an alternative treatment for the management of infection in VAP cases; however, in order to make a definite statement about the effectiveness of our proposed treatment, further studies with a cellular and molecular approach are required.

Our outcomes of the current trial cannot be included in all nebulized drugs plus G-CSF or to all subjects that are affected by other respiratory microorganisms and more detailed studies are needed for commendation.

Limitations of the study

The small sample of the patients and also single-center study were the main limitations of the present trial study.

Authors' contribution

Conceptualization: FK, FM, SY, AM.
Methodology: FK, BA.
Validation: FK, BA, SF.
Formal aanalysis: FK, BA.
Investigation: FK, BA, SF.
Resources: AM, SY, AH.
Data curation: FA, FK.
Writing–original draft: FK, FM, SY, AM.
Writing–review and editing: SF, BA, AH, SY, AM.
Visualization: FK, FM, BA.
Supervision: FM, FK.
Project administration: FM.

Conflicts of interest

The authors of present manuscript declare that there are no conflicts of interest**.**

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The study was approved by the ethics committee of the Isfahan University of Medical Sciences (#IR.MUI.MED.REC.1397.052) and registered in the Iranian Registry of Clinical Trials (# IRCT20150824023743N2, https://irct.ir/trial/41023). Informed consent was obtained from all the patients. This paper was extracted from the residential thesis of Fatemeh Mohajeri, department of infectious disease, Isfahan University of Medical Sciences. Moreover, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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