Original Article

The Effectiveness of Colistin/Rifampin Compared to Colistin/Meropenem in the Treatment of Ventilator-associated Pneumonia Caused by Carbapenem-resistant *Acinetobacter baumannii*: A Randomized Controlled Clinical Trial

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ABSTRACT

Objective: Treating ventilator-associated pneumonia (VAP) caused by carbapenem-resistant *Acinetobacter baumannii* (CRAB) is still a significant challenge. This study evaluated the effectiveness of the colistin/rifampin regimen compared to the usual colistin/meropenem regimen in treating patients with VAP caused by CRAB. **Methods:** In a randomized controlled clinical trial, the patients with CRAB-related VAP were randomly assigned to experimental (n = 21) and control (n = 24) groups. The first group received colistin 4.5 MIU IV infusion every 12 h and rifampin 300 mg PO every 12 h, and the second group received colistin with the same dose and meropenem 2 g IV every 8 h for 10 days. The clinical response (complete response, partial response, or treatment failure) and mortality rate at the end of the intervention were recorded and compared between the two groups. **Findings:** The complete response rate was higher (n = 8; 66.70%), and the failure rate was lower (n = 4; 26.70%) in the experimental group than in the control group (n = 4; 33.30%, and n = 11; 73.30%, respectively), but the differences were not statistically significant. The mortality rate was three patients in both experimental (14.28%) and control (12.50%) groups; however, the difference was not statistically significant (P = 0.860; odds ratio: 1.143, 95% confidence interval: 0.258–5.067). **Conclusion:** The colistin/rifampin combination can be considered an alternative regimen to colistin/meropenem in the treatment of VAP caused by CRAB.

Keywords: *Acinetobacter baumannii, Colistin, Meropenem, Rifampin, ventilator-associated pneumonia*

Introduction

Ventilator-associated pneumonia (VAP) represents one of the most common hospital-acquired infections,

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carrying a significant risk of morbidity and mortality.[1] VAP develops at least 48 h after endotracheal intubation and initiation of mechanical ventilation in intensive care unit (ICU) patients.[2] Gram-negative bacteria resistant to therapy have been responsible for most cases of VAP in recent years.[3] *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* show the most resistance[4] among Gram-negative organisms. *Acinetobacter* species are one of the primary pathogens responsible for healthcare-associated infections, which are related to high rates of morbidity and mortality globally, mainly because of their high capacity to develop resistance to antimicrobials.[5] Some species of *Acinetobacter*, especially *A. baumannii,* an opportunistic pathogen, show resistance to various antibiotics, including carbapenems.[6] The mortality rate from VAP caused by *A. baumannii* varies from 40% to 70%.[7,8] In 2017, *A. baumannii*, resistant to carbapenem, was placed on the critical group of the universal priority list of the World Health Organization for antibiotic-resistant bacteria, to mention the importance of research development and the urgency of new antibiotics.[9] Nowadays, *A. baumannii* is the most common cause of VAP in most regions.[9] Although the carbapenem-resistant *A. baumannii* (CRAB) is increasing but also cases of pan-drug-resistant *A. baumannii* have been reported.[10] Due to high resistance to common antibiotic agents, treatment of this pathogen is a significant concern.[11] Some approaches have been taken to deal with the multidrug-resistant (MDR) *A. baumannii*, such as combination therapy and using the synergistic effect of certain antibiotics with colistin and ampicillin/sulbactam against this pathogen. Combination therapy reduces the required antibacterial therapeutic doses, and as a result, it can reduce the risk of side effects and drug toxicity in patients.[12,13] Some *in vitro* and *in vivo* studies have reported the synergistic effect between rifampin and colistin against MDR *A. baumannii*.[14-16]

Since VAP is a well-known cause of death in hospitalized patients, treatment of cases caused by MDR *A. baumannii* is still a big challenge. Therefore, it is predicted that combination therapy of colistin and rifampin will be effective in the treatment of VAP caused by MDR *A. baumannii*. It is recommended that clinical research be conducted to find the best combination of antibiotics that have synergistic effects against this pathogen to attain the best result. Therefore, this study was planned to evaluate the effectiveness of the colistin/rifampin combination (which is shown to be synergistic) compared with the colistin/meropenem combination (which is usually used as the current standard antibiotic regimen) in the treatment of VAP caused by CRAB.

Methods

From November 2022 through December 2023, this randomized controlled clinical trial was carried out at Al-Zahra Hospital of Isfahan, affiliated with Isfahan University of Medical Sciences (IUMS), Iran.

The study population included patients with CRAB-related VAP hospitalized in the ICUs. The inclusion criteria consisted of (1) age over 18 years; (2) undergoing mechanical ventilation (intubation) for more than 48 h; (3) diagnosis of VAP; and (4) growth of carbapenem (meropenem)-resistant *A. baumannii* in the tracheal secretions culture.

The exclusion criteria were: (1) pregnancy; (2) breastfeeding; (3) history of allergy to colistin, rifampin, and/or meropenem; (4) acute respiratory distress syndrome; (5) active pulmonary tuberculosis; (6) simultaneous nonpulmonary bacterial or fungal infection; (7) creatinine clearance <60 mL/min according to the Cockroft–Gault formula; and (8) use of any other nephrotoxic drugs (e.g., vancomycin, any aminoglycoside, and amphotericin B).

Definitive diagnosis of VAP in a patient was made based on the following criteria: new or progressive infiltration on lung imaging, plus at least two of the following symptoms of infection:

(1) fever (temperature >38°C), (2) leukocytosis (white blood cell >12,000/mm^3), and (3) leukopenia (white blood cell <4000/mm^3), plus at least one of the following symptoms: (1) increased secretions of the respiratory tract and occurrence of purulent sputum with a higher need for suction, (2) crackles in lung auscultation, and (3) worsening of oxygenation (paO_2/FIO_2 ≤240), plus positive tracheal sample culture.[17]

Because the participants in this study were unconscious, the patient's relatives provided written informed consent.

Using the following sample size formula, at the confidence level of 95% and 80% test power and according to the results of a previous study,[18] based on the variance of the clinical pulmonary infection score (CPIS) values of 1.62 and 2.12 for the two treatment groups, respectively, and the effect size of 1.6 obtained by the mean difference of CPIS between the two groups, the sample size in each group was estimated to be 21 individuals:

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \left(\sigma_1^2 + \sigma_2^2\right)}{\left(\mu_1 - \mu_2\right)^2}$$

$$= \frac{\left(1.65 + 0.84\right)^2 \left(1.62^2 + 2.12^2\right)}{\left(4.2 - 5.8\right)^2} = 21$$

Sampling was done by aspiration of endotracheal secretions of patients. After suctioning the patients' tracheal secretions, about 2–3 mL of this sample was collected in a sterile sampling container and instantly sent to the microbiology laboratory of the hospital for culture, identification of the pathogen type, and determination of its antibiotic susceptibility by disk diffusion method using Clinical and Laboratory Standards Institute guidelines.[19] Then, the patient was included in the study if the culture yielded CRAB (detected by the meropenem disk 10 μg).

Before the study's implementation, the purpose of the current study was explained to patients or their relatives. They participated in the study if they agreed and signed a written informed consent form. The included patients were randomly and equally assigned to experimental and control groups using the block randomization method by blocks of four. The patient's demographic and clinical characteristics, including age, gender, underlying illnesses, cause of hospitalization, blood tests, disease status, or severity based on the scores of Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), and CPIS, and serum procalcitonin (PCT) levels were determined and recorded at the start of the trial. In the control group, meropenem 2 g as a 3-h IV infusion was administrated every 8 h along with a nine MIU loading dose of colistin by IV infusion, followed by 4.5 MIU IV infusion every 12 h for 10 days.[20] In the experimental group, rifampin 300 mg PO was administrated every 12 h along with the same dose of colistin as for the control group for 10 days.

To evaluate the patients, at the end of the intervention, the scores of APACHE II, SOFA, and CPIS were again calculated, and the serum PCT levels were again measured. The clinical response at the end of the trial was evaluated as the primary outcome variable and classified into three classes,[21] including complete response (improvement of all clinical symptoms including fever, leukocytosis, and purulent sputum), partial response (improvement of at least two of the mentioned clinical symptoms), and failure (continuation or worsening of the initial symptoms). The infectious disease specialist and intensive care physician evaluated and judged this item.

The secondary outcome variables were: (1) changes in the CPIS score at the end of the trial. This index estimated the severity of VAP by giving scores based on the clinical, radiographic, and microbiological characteristics of patients; (2) all-cause mortality rate at the end of intervention; (3) changes in the SOFA score at the 4th, 7th, and 10th (end) days of the study; (4) changes in PCT serum levels at the end of trial; (5) incidence of acute kidney injury (AKI) at the end of trial, considered as an increase in serum creatinine of 0.3 mg/dL or more within 48 h or raise of serum creatinine to ≥1.5 times the baseline value during the last 7 days, according to the definition of The Kidney Disease: Improving Global Outcomes.[22] The AKI stage (1, 2, or 3) was also determined.[22]

SPSS version 26 (IBM Corporation, United states, Armonk, New York) software was used for statistical analysis. Continuous quantitative variables were reported as mean ± standard deviation and qualitative variables as frequency (percentage). The Kolmogorov–Smirnov test was used for data distribution examination. Using the Chi-square test, the frequency distribution of qualitative variables was compared between the two groups. To compare quantitative parameters with normal and nonnormal distribution between the two groups, the independent samples *t*-test and Mann–Whitney *U* test were used, respectively. Furthermore, ANCOVA was used to compare the end-of-intervention values between the groups with the control of baseline values. In each analysis, the significance level was considered $P < 0.05$.

Results

During the study, 70 patients were evaluated for eligibility to participate in the intervention, and 48 patients were included based on the inclusion and exclusion criteria. They were randomly classified into experimental or control groups. In the control group, three individuals were excluded from the study due to death in the first 48 h of treatment [Figure 1].

Table 1 presents the patients' basic demographic and clinical information. As shown, there was no significant difference between the two groups regarding any baseline variables.

Table 2 compares the values of outcome variables of the patients in the two groups. As shown, even though CRP and PCT decreased in the experimental group in contrast to an increase in the control group, there was no significant difference between the two groups at the end of the intervention. Furthermore, while the CPIS score decreased in both groups at the end of the intervention, the reduction in the experimental group was significantly more than in the control group. Regarding SOFA, despite a trend toward a decrease and increase in the experimental and control groups, respectively, during the intervention, there was no significant difference between the groups in the evaluated time points and the trend of changes within the groups.

Table 3 compares the clinical responses of the two groups. Although the rate of complete response and

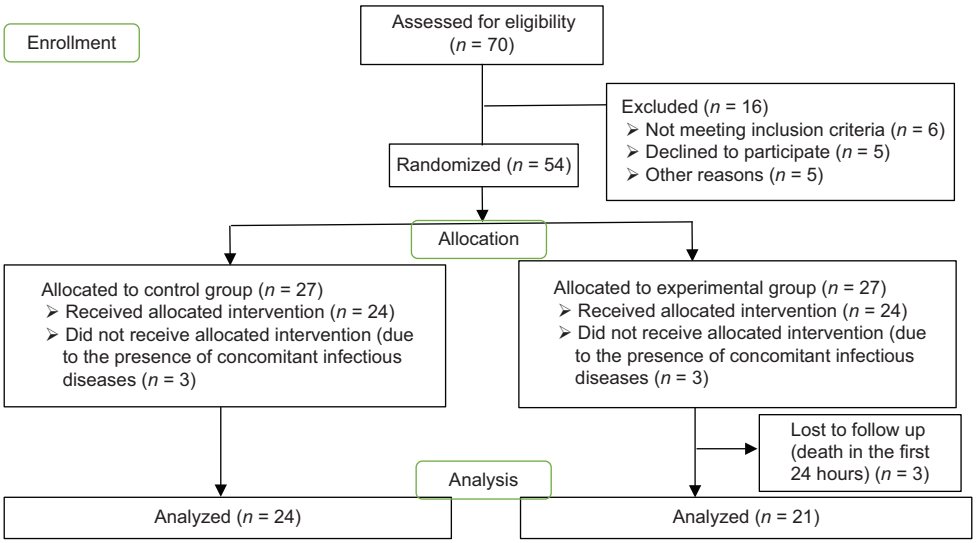

Figure 1: CONSORT flow diagram

Table 1: Baseline demographic and clinical characteristics of studied patients

Parameter	Experimental group (*n*=21)	Control group (*n*=24)	*P*
Age (years)	56.90±20.63	51.00±19.01	0.311*
Gender, *n* (%)			
Male	16 (76.2)	16 (66.7)	0.482**
Female	5 (23.8)	8 (33.3)	
APACHE II score	13.85±5.04	14.25±4.79	0.729*
SOFA score	5.38±1.88	5.12±1.39	0.163*
CPIS	7.00±1.26	6.29±1.08	0.056***
WBC (cells/mm^3)	9247.61±3833.87	9375.00±3976.69	0.752*
PCT (µg/L)	1.88±3.44	0.65±1.09	0.397***
ESR (mm/h)	85.92±38.07	109.33±26.91	0.106*
CRP (mg/L)	86.71±46.26	81.76±33.52	0.884*
Heart rate (beats/min)	95.09±14.14	96.41±18.78	0.982*
MAP (mmHg)	96.57±9.88	100.00±12.75	0.134*
Respiratory rate (breaths/min)	18.33±3.58	17.04±3.23	0.147***
PaO_2 (mmHg)	88.23±27.16	93.47±33.91	0.815*
Diagnosis, *n* (%)			
Multiple trauma	6 (50.00)	6 (50.00)	0.196**
CVA	3 (100.00)	0	
SAH/ICH/SDH	5 (55.60)	4 (44.40)	
LOC	3 (25.00)	9 (75.00)	
Cancer	4 (44.40)	5 (55.60)	

*Independent-samples *t*-test, **Chi-square test, ***Mann–Whitney *U*-test. The values are reported as mean±SD. SD=Standard deviation, APACHE=Acute physiology and chronic health evaluation, SOFA=Sequential organ failure assessment, CPIS=Clinical pulmonary infection syndrome, WBC=White blood cell, ESR=Erythrocyte sedimentation rate, CRP=C-reactive protein, MAP=Mean arterial pressure, CVA=Cerebrovascular accident, SAH=Subarachnoid hemorrhage, ICH=Intracerebral hemorrhage, SDH=Subdural hematoma, LOC=Loss of consciousness

treatment failure in the experimental group was higher and lower than in the control group, respectively, the difference was not statistically significant.

During the intervention, the all-cause mortality rate was three patients (14.28%) in the experimental group and three patients (12.5%) in the control group, and the difference was not statistically significant (P = 0.860; odds ratio [OR]: 1.143, 95% confidence interval [CI]: 0.258–5.067).

Although the incidence of AKI in the experimental group (8 patients; 38.09%) was more than that in the control group (6 patients; 25%), the difference was not statistically significant (P = 0.344; OR: 1.524, 95% CI: 0.631–3.680). Of note, most cases of AKI in

Table 2: The changes in outcome parameters during the study and their comparison between the groups

Parameter	Time	Experimental (*n*=21)	Control (*n*=24)	*P*
CRP (mg/dL)	Baseline	86.71±46.26	81.76±33.52	0.884*
	End	84.40±22.83	90.40±54.62	0.714**
CPIS	Baseline	7.00±1.26	6.29±1.08	0.056*
	End	3.57±1.35	4.78±0.86	0.030**
PCT	Baseline	1.88±3.44	0.65±1.09	0.397*
	End	0.32±0.41	0.83±2.46	0.404**
SOFA	Baseline	5.38±1.88	5.12±1.39	0.163***
	Day 4	5.20±2.80	5.41±2.14	0.099***
	Day 7	4.66±2.61	5.04±1.77	0.587***
	End	4.29±2.59	5.15±1.75	0.238***
P		0.143****	0.952****	0.339****

*Mann–Whitney *U*-test, **ANCOVA test, ***Independent-samples *t*-test, ****Repeated measures ANOVA. The values are reported as mean±SD. SD=Standard deviation, CPIS=Clinical pulmonary infection score, PCT=Procalcitonin, SOFA=Sequential organ failure assessment, CRP=C-reactive protein

Table 3: The rate of each type of clinical response in study patients and their comparison between the groups

Groups (*n*)	Clinical response			
	Complete	Partial	Failure	*P*
Experimental (21)	8 (66.70)	9 (50.00)	4 (26.70)	0.110*
Control (24)	4 (33.30)	9 (50.00)	11 (73.30)	

*Chi-square test. The values are presented as frequency (%)

both groups were Stage 1, including six patients (75% of AKI cases) in the experimental group versus five patients (83.30% of AKI cases) in the control group, followed by one case of Stage 2 in each group (12.5% vs. 16.7%, respectively) and one case of Stage 3 (12.5%) only in the experimental group. However, there was no significant difference in the distribution of AKI stages between the two groups ($P = 0.663$).

Discussion

This study evaluated the effectiveness of the colistin/rifampin combination compared to the colistin/meropenem combination in treating VAP caused by CRAB in 45 patients.

The clinical response of the patients indicated that in the colistin/rifampin group, a higher percentage of patients had a complete response. Furthermore, the treatment failure rate was higher in the colistin/meropenem group. Although the colistin/rifampin regimen may have been superior, these differences were not statistically significant. Therefore, according to the results of this study, the effectiveness of these two regimens in the clinical improvement of VAP caused by CRAB is the same. However, there was a trend toward the better efficacy of the colistin/rifampin regimen.

The mortality rate of patients in the experimental and control groups was similar, indicating that these two regimens were equally effective.

Few similar studies have evaluated the combination of colistin and rifampin in treating VAP. In a study conducted in 2018 by Park *et al*., the combination of colistin/rifampin was effective in the treatment of VAP caused by CRAB so that microbiological response (MR) in the combination group was 100% in comparison to 40% in the group that received colistin alone. Only nine patients participated in this study, and the number of patients was very few.[15] In another study conducted in 2012 by Aydemir *et al*., although the combination of colistin/rifampin vs. colistin alone improved clinical, laboratory, radiological, and MR rates in VAP patients caused by CRAB, none of these differences were statistically significant. It should be noted that compared to our study, the mortality rate in this study was much higher (38.1% in the experimental group and 63.6% in the control group).[16] In the study by Bassetti *et al*., the combination of colistin and rifampicin appeared to be an effective and safe combination therapy for severe infections due to MDR *A. baumannii*. Only 29 patients participated in this study, and the mortality rate was 21% (6 patients), which was higher than that in our research, and the clinical response rate was 76%, almost the same as our results.[23]

Several laboratory and clinical studies have shown the synergistic effect of colistin and rifampin on resistant Gram-negative pathogens.[15,16] A possible mechanism for this synergistic effect is that colistin degrades the outer membrane of the bacteria, facilitating the penetration of rifampin into the bacteria. Rifampin is hydrophobic and typically cannot penetrate Gram-negative bacteria.[24]

The current study evaluated several parameters, including CRP, SOFA, CPIS, and PCT, as secondary outcome values.

The SOFA score does not help determine the type of treatment and evaluation of the treatment outcomes. This score only helps identify patients who have a high risk of death due to infection. This index was determined to ensure that the patients in the two groups had the same mortality risk. As shown, SOFA scores were statistically equal between the two groups at the beginning of the study, suggesting that the patients in the two groups were similar in terms of organ involvement and critical condition severity at baseline. Although the SOFA score in the experimental group showed a decreasing trend during the study, these changes were insignificant. Furthermore, in none of the evaluated times, there was no significant difference between the two groups in terms of the SOFA. However, the results showed the

tendency of the colistin/rifampin regimen to reduce this index, which indicates a reduction in organ failure during the intervention. In contrast, this index showed an almost unchanged trend in the colistin/meropenem group.

The parameter PCT is used for rapid diagnosis of systemic bacterial infections. Other inflammatory biomarkers, including CRP, cannot accurately distinguish bacterial infection from nonbacterial infection, but PCT can detect bacterial infections with a specificity of about 80%.[25] In VAP, the cutoff level for this indicator is considered to be 0.1–0.25 ng/mL, and it is recommended to discontinue antibiotics if PCT values reach <0.1 ng/mL during treatment and clinical improvement has been achieved.[25] The anti-inflammatory effect of rifampin has been shown previously; this drug exerts its anti-inflammatory effect by inhibiting the production of inflammatory cytokines, including interleukins 1β, 6, 8, and 10 and also by inhibiting the production of tumor necrosis factor alpha TNF-α.[26] Therefore, in this study, the significant reduction of PCT in the colistin/rifampin group could show the adequate treatment and effective lowering of the pathogen load in the lung.

This study also calculated and analyzed the patients' CPIS score or CPIS. Although the CPIS score decreased in both groups at the end of the intervention, consistent with the clinical response, the decrease in the experimental group was significantly more significant than in the control group. This shows that the combination of colistin and rifampin better-controlled pneumonia parameters, including tracheal secretions, chest infiltrates, PaO2/FiO2 ratio, and microbial growth.

In the present study, the rate of AKI in the experimental group was slightly more than in the control group. Although the difference was not statistically significant, this result can be a warning for renal toxicity of the colistin/rifampin combination. It should be investigated in future studies with a larger sample size. In addition to common side effects such as hepatotoxicity, rifampin has rare side effects, including kidney injury. Although this complication is rare, since 1976, there have been several reports regarding the occurrence of kidney injury after taking rifampin.[27] Rifampin-induced nephrotoxicity often appears as acute tubular necrosis, and there is a hypothesis that immune response plays a role in the occurrence of this complication.[28] However, simultaneous administration of rifampin with other nephrotoxic drugs (e.g., colistin) can exacerbate this complication in the patients. Therefore, during administering this combination, the patients should be constantly monitored for signs and symptoms of nephrotoxicity.

The study's most critical limitations were the small sample size, open-label nature (no blinding), and exclusion of patients with possible sepsis, which may affect the evaluated outcome variables. However, this is the first relatively well-controlled clinical trial showing the acceptable effectiveness of the colistin/rifampin regimen for treating CRAB-related VAP. This regimen could be used in place of the colistin/meropenem combination to save meropenem and in times of meropenem shortage in the country. Furthermore, this regimen could be evaluated for infections due to colistin-resistant *A. baumannii*.

According to the results of the present study, both colistin/rifampin and colistin/meropenem regimens had the same effects on the clinical improvement of VAP in the patients. It is worth considering that although the critical outcome factors in this study did not significantly vary between the two groups, in the colistin/rifampin group, the rate of complete clinical response was more remarkable, and the treatment failure rate was lower than in the control group. On the other hand, compared to rifampin, meropenem is more expensive and can be associated with more drug resistance. Regarding the disadvantages caused by the overuse of meropenem, such as the occurrence of resistance to carbapenems and its occasional shortages in the pharmaceutical market, and the same effectiveness of the two tested regimens, it is possible to consider the rifampin/colistin combination as an alternative regimen to meropenem/colistin in the treatment of VAP caused by CRAB.

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Authors' Contribution

R. Soltani designed the study, interpreted the results, and performed the statistical analysis. M. Kazemi collected the patients' data and drafted the manuscript. B. Alikiaei and F. Khorvash selected the patients according to the inclusion criteria, prescribed the study drugs, and evaluated the patients' outcomes. F. Shafiee performed and interpreted the microbiological studies. All authors approved the final manuscript.

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Conflicts of interest

There are no conflicts of interest.

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