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Evaluation of the combination treatments with intravenous fosfomycin for carbapenem-resistant *Klebsiella pneumoniae*

Uğur Önal[1*], Nazmiye Ülkü Tüzemen[2], Pınar Küçükdemirci Kaya[3], Remzi İşçimen[3], Nermin Kelebek Girgin[3], Cüneyt Özakın[2], Ferda Şöhret Kahveci[3], Halis Akalın[1]

SUMMARY

OBJECTIVE: The aim of this study was to evaluate the combination treatments with intravenous fosfomycin for carbapenem-resistant *Klebsiella pneumoniae* infections in a tertiary-care center.

METHODS: Between December 24, 2018 and November 21, 2022, adult patients diagnosed with bloodstream infection or ventilator-associated pneumonia due to culture-confirmed carbapenem-resistant *Klebsiella pneumoniae* in the anesthesiology and reanimation intensive care units were investigated retrospectively.

RESULTS: There were a total of 62 patients fulfilling the study inclusion criteria. No significant difference was recorded in 14- and 30-day mortality among different types of combination regimens such as fosfomycin plus one or two antibiotic combinations. Hypokalemia (OR:5.651, 95%CI 1.019–31.330, p=0.048) was found to be a significant risk factor for 14-day mortality, whereas SOFA score at the time of diagnosis (OR:1.497, 95%CI 1.103–2.032, p=0.010) and CVVHF treatment (OR:6.409, 95%CI 1.395–29.433, p=0.017) were associated with 30-day mortality in multivariate analysis.

CONCLUSION: In our study, high mortality rates were found in patients with bloodstream infection or ventilator-associated pneumonia due to carbapenem-resistant *Klebsiella pneumoniae*, and no significant difference was recorded in 14- and 30-day mortality among different types of combination regimens such as fosfomycin plus one or two antibiotic combinations.

KEYWORDS: Fosfomycin. Bloodstream infection. Ventilator-associated pneumonia. *Klebsiella pneumoniae*.

INTRODUCTION

Antimicrobial resistance is a global threat, and carbapenem-resistant *Klebsiella pneumoniae* (CRKP) represents a significant challenge that has important regional differences in clinical outcomes with limited treatment options[1]. According to the *in vitro* studies, different degrees of synergy or bactericidal activities were recorded with various treatment combinations for the infections due to CRKP[2].

Currently, there are limited data on the efficacy and safety of intravenous fosfomycin in clinical practice among critically ill patients. Therefore, we aimed to evaluate the risk factors for mortality (14 and 30 days) among combination treatments with intravenous fosfomycin for CRKP infections in a tertiary-care center.

METHODS

Between December 24, 2018 and November 21, 2022, adult patients diagnosed with bloodstream infection (BSI) or ventilator-associated pneumonia (VAP) due to culture-confirmed CRKP in the anesthesiology and reanimation intensive care unit (ICU) of a 900-bed tertiary care university hospital were investigated retrospectively. Primary outcomes were defined as 14- and 30-day mortality.

Bloodstream infection was classified as primary (a laboratory-confirmed BSI that is not secondary to another site infection) or secondary, which is thought to be seeded from a site-specific infection at another body site[3]. Pneumonia was defined using the criteria of the presence of new or progressing infiltrates in the chest radiography and at least two of the following: (I) temperature >38°C; (II) leukocytes >10,000/mm^3 or <4,000/mm^3; (III) decline in oxygenation; and (IV) purulent bronchial secretion (leukocytes>25) with the presence of ≤10 epithelial cells in the Gram staining of deep endotracheal aspirate (ETA) (10´), and VAP was defined as pneumonia that developed after more than 48 h intubation and received mechanical ventilation[4]. Immunosuppression was defined as having a congenital condition or transplantation, an illness, or taking medications

[1]Uludag University, Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology – Bursa, Turkey.
[2]Uludag University, Faculty of Medicine, Department of Microbiology – Bursa, Turkey.
[3]Uludag University, Faculty of Medicine, Department of Anesthesiology and Reanimation – Bursa, Turkey.
*Corresponding author: uguronal@uludag.edu.tr
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(chemotherapy, corticosteroids as receiving ≥20 mg prednisone or equivalent per day for at least 2 or more weeks, calcineurin inhibitors, and cytotoxic agents)[5]. INCREMENT (5 points for severe sepsis or septic shock, 4 points for Pitt score ≥6, 3 points for Charlson comorbidity index ≥2, and 3 points for source of BSI other than urinary or biliary tract) score was calculated at the diagnosis of infection[6].

Inclusion criteria:

- Patients ≥18 years of age,
- Meeting the diagnostic criteria for BSI or VAP,
- The presence of a positive culture results in CRKP.

Exclusion criteria:

- Colonizations that were not causing clinical signs or symptoms and/or inflammation resulting from tissue response to injury or stimulation by noninfectious agents,
- Rather than intravenous fosfomycin, patients are treated with combinations of ≥3 antimicrobials that can be used for resistant gram-negative pathogens.

Statistical analyses were performed using the SPSS software version 28.0 (IBM Corp., Armonk, NY, United States). The Student's t-test was used for the analysis of parametric variables. In univariate analysis, a p-value below 0.05 was considered to be statistically significant and included in binary logistic regression analysis.

The study was approved by the Uludag University Ethics Committee with a decision number of 2023-4/10 on February 21, 2023.

RESULTS

There were a total of 62 patients fulfilling the study inclusion criteria. The most common comorbidities were recorded as hypertension (51.6%), diabetes mellitus (45.2%), and malignancy (30.6%), respectively. The mean duration of hospitalization in the ICU was found to be 57.35±6.57 days. A total of 33 patients (53.2%) had BSI, and 29 patients (46.8%) had VAP. Overall mortality rates for 14 and 30 days were recorded as 35.5 and 54.8%, respectively. In the subgroup of BSI, the overall mortality rates for 14 and 30 days were recorded at 30.3 and 57.6%. On the contrary, in the subgroup of VAP, overall mortality rates for 14 and 30 days were recorded at 41.4 and 51.7%, respectively. Univariate analysis for 14- and 30-day mortality is summarized in Table 1.

Multivariate regression analysis for 14- and 30-day mortality is shown in Table 2. Hypokalemia was found to be a significant risk factor (odds ratio (OR): 5.651, 95%CI 1.019–31.330, p=0.048) for 14-day mortality. One point increase in SOFA score at the time of diagnosis (OR: 1.497, 95%CI 1.103–2.032, p=0.010) and CVVHF treatment (OR: 6.409, 95%CI 1.395–29.433, p=0.017) were associated with 30-day mortality.

All of the patients received intravenous fosfomycin with a combination treatment. There was no significant difference in 14- and 30-day mortality among different types of combination regimens such as one or two antibiotic combinations, meropenem-containing regimens, colistin/polymyxin B-containing regimens, and aminoglycoside-containing regimens (Tables 1 and 3).

In the subgroup analysis of patients with BSI (n=33), patients with 14- and 30-day mortality had higher INCREMENT scores than the survivors (patients with a 14-day mortality rate of 13.30±0.77 vs. survivors of 10.39±0.74 had a p-value of 0.025, and those with a 30-day mortality rate of 12.47±0.62 vs. survivors of 9.64±1.02 had a p-value of 0.019).

Hypernatremia was recorded in 17 patients (27.4%) as the most common side effect, followed by hypokalemia in 14 patients (22.5%), and hypernatremia was not significantly affected by using either normal saline or 5% dextrose solution (15/17 vs. 2/17, p=0.712).

DISCUSSION

Although new agents such as ceftazidime-avibactam, meropenem-vaborbactam, and cefiderocol were recommended by guidelines for the treatment of carbapenem-resistant enterobacterial infections, these antibiotic options are still not available, especially in most low- and middle-income countries[7]. The potential efficacy of various combination treatments with intravenous fosfomycin for CRKP has been described in a very limited number of studies with a low number of patients;, therefore, our study highlights the efficacy and safety profiles of intravenous fosfomycin treatment for critically ill patients with BSI or VAP due to CRKP.

A multicenter, observational, and prospective study was performed about the outcomes of critically ill patients treated with fosfomycin for infections due to carbapenemase-producing gram-negative bacteria, and fosfomycin was combined (fosfomycin plus one, two, or three antibiotics in 18 (37.5%), 26 (54.2%), and 4 patients (8.3%)) with colistin in 32 patients (66.7%), with tigecycline in 19 patients (39.6%), with gentamicin in 15 patients (31.3%), with meropenem in 12 patients (25.0%), and with piperacillin/tazobactam in 4 patients (8.3%), respectively. Overall, 28-day mortality was found to be 37.5%,

Table 1. Univariate analysis for 14- and 30-day mortality.

Variables		14-day mortality		p-value	OR	95%CI	30-day mortality		p-value	OR	95%CI
		Present	Absent				Present	Absent			
Age	(years)	53.45±4.17	64.10±2.51	**0.029***	0.966	0.937–0.997	56.74±3.13	64.68±3.15	0.087	–	–
Gender	Male Female	12 10	21 19	0.877	–	–	19 15	14 14	0.644	–	–
Hypertension	Present Absent	6 16	26 14	**0.006***	0.202	0.064–0.632	14 20	18 10	0.073	–	–
Malignancy	Present Absent	11 11	8 32	**0.017***	4.000	1.280–12.502	12 22	7 21	0.383	–	–
Immunosuppression	Present Absent	13 9	7 33	**0.001***	6.810	2.097–22.115	15 19	5 23	**0.032***	3.632	1.115–11.824
Bacteremia	Present Absent	10 12	23 17	0.365	–	–	19 15	14 14	0.644	–	–
CVVHF treatment	Present Absent	10 12	11 29	0.157	–	–	17 17	4 24	**0.005***	6.000	1.712–21.025
APACHE-II score (at the diagnosis of infection)	(point)	25.77±1.59	21.10±1.04	**0.021***	1.105	1.015–1.203	24.53±1.20	20.61±1.31	**0.040***	1.091	1.004–1.185
SOFA score (at the diagnosis of infection)	(point)	10.95±0.81	7.90±0.48	**0.004***	1.303	1.091–1.558	10.68±0.61	6.93±0.48	**<0.001***	1.511	1.200–1.902
Hypernatremia	Present Absent	3 19	14 26	0.081	–	–	10 24	7 21	0.699	–	–
Hypokalemia	Present Absent	9 13	5 35	**0.014***	4.846	1.368–17.171	10 24	4 24	0.164	–	–
Daily fosfomycin dose (adjusted for creatinine clearance)	(g/day)	12.86±0.82	11.86±0.74	0.399	–	–	12.08±0.69	12.37±0.92	0.802	–	–

*p<0.05.

Table 2. Multivariate analysis for mortality.

Variables	14-day mortality			30-day mortality		
	p-value	OR	95%CI	p-value	OR	95%CI
Immunosuppression	0.311	–	–	0.075	–	–
SOFA score (1 point increase at the diagnosis of infection)	0.537	–	–	**0.010***	**1.497**	**1.103–2.032**
APACHE-II score (at the diagnosis of infection)	0.181	–	–	0.985	–	–
CVVHF treatment				**0.017***	**6.409**	**1.395–29.433**
Age	0.372	–	–			
Hypertension	0.083	–	–			
Malignancy	0.776	–	–			
Hypokalemia	**0.048***	**5.651**	**1.019–31.330**			

Nagelkerke R^2: 0.498 (14-day mortality); Nagelkerke R^2: 0.497 (30-day mortality). *p<0.05. Bold values were used for mentioning only the statistically significant results.

but in sub-group analysis, 28-day mortality was shown to be 43.5% for the CRKP group (n=23)[8]. Aysert-Yildiz et al., investigated a total number of 94 CRKP-infected patients treated with intravenous fosfomycin, and they revealed that favorable clinical response rates for combination treatments including meropenem and polymyxins as 66.6% (n=9) and 63.6%

Table 3. Combination treatments and mortality.

Combination type	n (%)	14-day mortality	30-day mortality
Combination with one antibiotic	27 (43%)	6 (22.2%)	11 (40.7%)
Fosfomycin plus meropenem	12 (19%)	3 (25%)	5 (41.6%)
Fosfomycin plus colistin/polymyxin B	7 (11%)	2 (28.5%)	4 (57.1%)
Fosfomycin plus amikacin/gentamycin	3 (5%)	1 (33.3%)	1 (33.3%)
Fosfomycin plus others*	5 (8%)	0 (0%)	1 (20%)
Combination with two antibiotics	35 (57%)	16 (45.7%)	23 (65.7%)
Fosfomycin plus meropenem plus colistin/polymyxin B	14 (23%)	7 (50%)	10 (71.4%)
Fosfomycin plus meropenem plus amikacin/gentamycin	9 (15%)	3 (33.3%)	4 (44.4%)
Fosfomycin plus colistin/polymyxin B plus amikacin/gentamycin	2 (3%)	0 (0%)	1 (50%)
Fosfomycin plus others*	10 (16%)	6 (60%)	8 (80%)

*Others: ceftazidim/avibactam, cefoperazone/sulbactam, tigecycline, TMP/SMX, ciprofloxacin, and levofloxacin.

(n=11) for bacteremia; 62.5% (n=16) and 60% (n=15) for pneumonia, respectively. In addition, they showed that all of the combination treatments had a similar clinical response rates for different types of infections except the tigecycline combination for pneumonia[9]. Perdigao Neto et al., described a prospective series of 13 patients (treated with fosfomycin) who had infections (BSI, n=11) due to β-lactams and colistin-resistant gram-negative bacteria (*K. pneumoniae*, n=9), and they showed that meropenem (82% synergism *via* time-kill assay) was the most commonly used antibiotic in combination with fosfomycin (n=10), with a cure rate of 70%[10]. Oliva et al., evaluated the effect of the ceftazidime/avibactam plus fosfomycin combination in the treatment of BSIs caused by CRKP, and although there was no difference in 30-day overall mortality, they showed a lower rate of subsequent CRKP or secondary infections than other ceftazidime/avibactam-based regimens in fosfomycin combination group[11]. In our study, we also found no statistically significant difference in 14- and 30-day mortality among different types of combination regimens such as one or two antibiotic combinations, meropenem-containing regimens, colistin/polymyxin B-containing regimens, and aminoglycoside-containing regimens.

In Turkey, Sengel et al., showed that the combination of fosfomycin with meropenem was found to be more synergistic (15/17 strains, 88%) than amikacin (29%) or colistin (41%) combinations against OXA-48 and/or New Delhi metallo-beta-lactamase (NDM)-producing CRKP for blood isolates despite very higher MICs for meropenem and fosfomycin[12]. On the contrary, another *in vitro* study evaluated 50 CRKP blood culture isolates regarding synergism and showed a synergy for fosfomycin-meropenem and fosfomycin-colistin combinations in 20 and 16% of the isolates, respectively[13]. Although molecular data about carbapenem resistance profiles was not included in our study, Zarakolu et al., investigated 131 CRKP bloodstream isolates collected from patients in three university hospitals, including our center, and they found that OXA-48 was the most prominent carbapenemase type (70.9%), followed by NDM (20.6%) and KPC (15.2%) types[14].

Although intravenous fosfomycin has a good safety profile for the treatment of CRKP infections, Aysert-Yildiz et al., showed common adverse events with intravenous fosfomycin treatment as hypokalemia (37.2%) and hypernatremia (22.3%)[9]. Pontikis et al., also investigated the side effects of parenteral fosfomycin, and they revealed severe hypokalemia in 10 patients (15.2%) as the main adverse event[8]. In our study, we found hypernatremia in 17 patients (27.4%) as the most common side effect, followed by hypokalemia in 14 patients (22.5%). In addition, the hypernatremia side effect was not significantly affected by using either normal saline or 5% dextrose solution (15/17 vs. 2/17, p=0.712). A retrospective cohort study among 309 critically ill patients treated with intravenous fosfomycin showed that hypokalemia was the most observed adverse event in 62.1% of cases, and regarding 30-day mortality, hypokalemia incidence was not significantly different between the survivors and nonsurvivors[15]. Similar to this study, we also found no significant difference for the hypokalemia side effect in terms of 30-day mortality. However, the presence of hypokalemia as a side effect of intravenous fosfomycin treatment was associated with 14-day mortality in our study.

A study among 384 patients with CPKP bacteremia in the ICU reported that an INCREMENT score ≥10 showed a sensitivity of 98.0% and a negative predictive value of 98.7% with an area under curve (0.800) comparable to other scores such as SOFA (0.815)[6]. In our study, we also found higher INCREMENT scores for patients with 14- and 30-day mortality

in the subgroup of BSIs. A prospective and multicentre observational cohort study about BSIs due to CRKP showed that SOFA score and immunosuppression were significant predictors of 30-day mortality (44%)[16]. Similar to these findings, we also found that a higher SOFA score at the time of infection diagnosis was associated with 30-day mortality in multivariate analysis. A study about the concentration-versus-time profile of fosfomycin in CVVHF with 12 anuric intensive care patients revealed that a regimen of 8 g every 12 h should be appropriate for patients undergoing CVVHF with a fosfomycin-susceptible pathogen[17]. In our study, similar to patients with normal renal functions, a daily fosfomycin dose of 16 g (divided into 2 doses) was preferred in patients undergoing CVVHF. In multivariate analysis of our study, CVVHF treatment was significantly associated with 30-day mortality. We believe that renal dose adjustments of the treatments, such as antibiotics used in combination, may have an impact on these results, and measurement of antibiotic serum levels may contribute to the optimal management of critically ill patients with CVVHF treatment.

Our study has several limitations. The main limitation is that this is a retrospective study with a small number of patients in a single center. Therefore, confounding factors for the endpoint to assess the effect of each combination treatment could not be identified. Finally, although the OXA-48 is the most prominent carbapenemase type according to a multicenter study from Turkey, including our hospital data, molecular identification of carbapenemase types could not be performed in our study.

CONCLUSION

In our study, high mortality rates were found in patients with BSI or VAP due to CRKP, and no significant difference was recorded in 14- and 30-day mortality among different types of combination regimens such as fosfomycin plus one or two antibiotic combinations. Multivariate regression analysis showed that a higher SOFA score and CVVHF treatment were associated with 30-day mortality. We believe that our study may support further investigation of parenteral fosfomycin in the target patient population, including patients with BSI and VAP due to CRKP.

AUTHORS' CONTRIBUTIONS

UÖ: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **HA:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Supervision, Visualization. N**ÜT:** Data curation, Formal Analysis, Investigation, Resources, Validation, Visualization. P**KK:** Data curation, Formal Analysis, Investigation, Resources, Validation, Visualization. **Rİ:** Data curation, Formal Analysis, Investigation, Resources, Validation, Visualization. N**KG:** Data curation, Formal Analysis, Investigation, Resources, Validation, Visualization. **CÖ:** Data curation, Formal Analysis, Investigation, Resources, Validation, Visualization. **FŞK:** Data curation, Formal Analysis, Investigation, Resources, Validation, Visualization.

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