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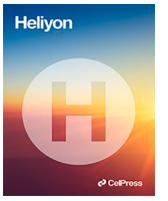

Research article

Effect of continuous renal replacement therapy on the clinical efficacy and pharmacokinetics of polymyxin B in the treatment of severe pulmonary infection

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ABSTRACT

Objective: This study aimed to evaluate the pharmacokinetics of polymyxin B in patients with ventilator-associated pneumonia caused by multi-drug resistant bacteria, and to analyze the effect of continuous renal replacement therapy (CRRT) on pharmacokinetics of polymyxin B.

Methods: Thirty-five patients with ventilator-associated pneumonia caused by multi-drug resistant bacteria admitted to our hospital from June 2021 to January 2022 were selected as the subjects. The patients were divided into the standard group (n = 20) and the non-standard group (n = 15) based on the factors affecting the compliance of polymyxin B plasma concentration. The patients received with polymyxin B and the plasma concentration was monitored. According to the monitoring results, they were divided into the standard group and the non-standard group, to analyze the influencing factors of polymyxin B on the blood concentration. Besides, the patients were then divided into the control group (n = 28) and the observation group (n = 7) according to whether the patients received CRRT treatment. Patients in the control group treated with polymyxin B alone, while patients in the observation group received with polymyxin B and CRRT. The general data of patients in the two groups were compared. The levels of plasma concentration of polymyxin B measured before the next administration (C_{min}), peak plasma concentration of polymyxin B measured immediately after end of infusion (C_{max}) and intermediate plasma concentration measured 6 h after administration (midpoint of the dosing interval) ($C_{1/2t}$) were detected and compared between the two groups. Correlation between pharmacokinetics and efficacy was analyzed by Spearman correlation. The incidence of complications and the 28-day mortality rate of the two groups were recorded.

Results: The age, body mass index (BMI) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores in the non-standard group were higher than these in the standard group ($p < 0.05$). BMI and APACHE II scores were independent risk factors affecting the pharmacokinetics of polymyxin B in patients with severe pulmonary infection ($p < 0.05$). There were no significant differences in age, BMI, APACHEII score, alanine aminotransferase level, aspartate aminotransferase level, albumin level, gender and diabetes ratio between the control group and the observation group ($p > 0.05$). The levels of C_{min}, C_{max}, and $C_{1/2t}$ in the observation group were lower than these in the control group ($p < 0.001$). The response rate was 50.00% in the control group and 36.36% in the observation group ($p > 0.05$). The levels of C_{min}, C_{max}, and $C_{1/2t}$ in the

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observation group were no significant correlation with the clinical efficacy ($p > 0.05$), while these in the control group were positive correlation with the clinical efficacy ($r = 0.485$, $p < 0.05$). There was no significant difference in the incidence of skin pigmentation, nephrotoxicity and 28-day mortality between the two groups ($p > 0.05$).

Conclusion: In patients with ventilator-associated pneumonia not receiving multidrug-resistant bacteria, the rate of achieving blood drug concentration with the usual recommended dose of polymyxin B was satisfactory. However, the proportion of patients with a 6-h plasma concentration exceeding the maximum plasma concentration was high. BMI and APACHE II scores were important factors affecting the pharmacokinetics of polymyxin B. In patients undergoing CRRT, the plasma concentration of polymyxin B was significantly reduced, suggesting that in patients with severe disease, plasma concentration monitoring played an important role in drug efficacy and patient safety. In patients treated with CRRT, the dose of polymyxin B may need to be increased.

1. Introduction

Severe pulmonary infection, also known as severe pneumonia, refers to serious complications or toxic symptoms in case of pulmonary infection. Moreover, in severe cases, respiratory distress syndrome (ARDS) and diffuse intravascular coagulation (DIC) can also occur, with a mortality rate of up to 30%–50%, which seriously threatens the life safety of patients [1,2].

Polymyxin B is a common non-ribosomal antibiotic used in clinical practice that kills bacteria by destroying bacterial membranes. At present, it is common to use for the treatment of severe lung infections [3,4]. However, serious side effects have been reported in polymyxin B, including nephrotoxicity, neurotoxicity, and hypersensitivity. The study has shown that patients with intra-abdominal infections received with polymyxin B treatment that developed diffuse darkening of the skin (skin pigmentation), most prominently on the face and forearms, which peaked at about 2 weeks [5]. Polymyxin B is mainly excreted by the kidneys, and plasma concentrations may be too high when the patients have some degree of renal decline. Continuous renal replacement therapy (CRRT) is a treatment modality that provides hemodialysis function around the clock. Compared with intermittent hemodialysis, CRRT plays an important role in maintaining hemodynamic stability and removing metabolic waste and cytotoxins from the body [6,7].

At present, clinical studies mainly focus on the treatment of non-CRRT severe pulmonary infections with polymyxin B, and there are few studies on the effect of CRRT on the pharmacokinetics and efficacy of polymyxin B. In this study, 35 patients with ventilator-associated pneumonia caused by multidrug-resistant bacteria admitted to our hospital from June 2021 to January 2022 were selected as the subjects, to analyze the effect of CRRT on clinical efficacy and pharmacokinetics of polymyxin B in the treatment of severe pulmonary infection.

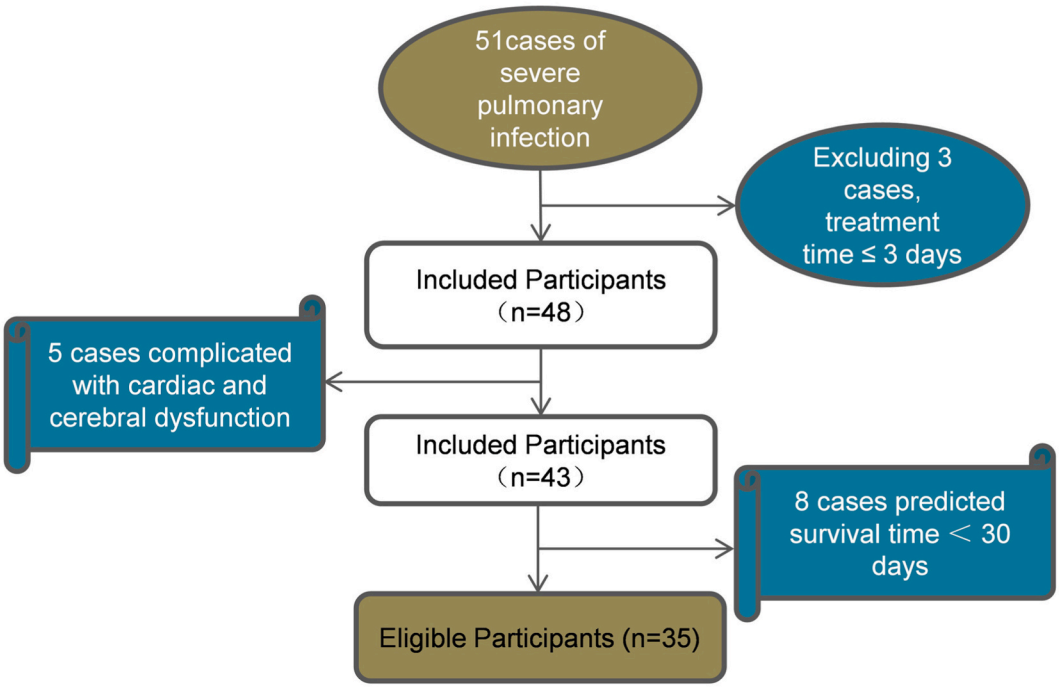

Fig. 1. Screening process of patients.

2. Materials and methods

2.1. General information

Thirty-five patients with ventilator-associated pneumonia caused by multidrug-resistant bacteria admitted to our hospital from June 2021 to January 2022 were selected as the subjects, and the screening process of patients was shown in Fig. 1. Inclusion Criteria [1]: All patients met the diagnostic criteria for severe pulmonary infection published by the Infectious Diseases Society of America and the American Thoracic Society [8]. [2] All patients were aged between 18 and 85 years [3]. All patients were bilateral or multiple lobes of the lungs detected by imaging [4]. All patients were complicated by symptoms such as impaired consciousness, respiratory rate of more than 30 breaths/min, and he ratio of arterial partial pressure of oxygen to inhaled oxygen concentration ratio of less than 300 [5]. All patients and their families signed the informed consent form. Exclusion Criteria [1]: Lactating or pregnant women [2]. Patients with malignant tumors [3]. Treatment duration of patients $\leq$3 d and predicted survival time of patients <30 d [4]. Patients who were allergic to the drugs in this trial [5]. Patients with severe dysfunction of vital organs such as heart and brain. The patients were divided into the control group (n = 28) and the observation group (n = 7) according to the treatment mode. All the procedures have been approved by the Ethics Committee of The Third People's Hospital of Chengdu (Approval number: 2021S-15).

2.2. Treatments

Patients in the control group received with polymyxin B sulfate for injection (purchased from SPH No. 1 Biochemical & Pharmaceutical Co., Ltd.; Approval number: GYZZH31022631; strength: 500,000 units) via intravenous drip for about 1 h with a loading dose of 15,000 U/Kg for the first dose and a maintenance dose of 20,000 U/Kg/d, twice daily.

Patients in the observation group received with CRRT on the basis of the treatment of the control group. CRRT was performed by using a continuous renal replacement therapy machine (Aquarius [GE-F082-00]) with a treatment mode of the continuous Veno-Venous Hemofiltration (CVVH). The vascular access was an intravenous catheter for large-bore double-lumen blood purification in the femoral vein. The therapeutic dose was set at 35 ml/kg/h and the blood flow rate was set at 200 ml/min. The dilution ratio of the replacement fluid before and after the filter were 90% and 10%, respectively. Patients without active bleeding were anticoagulated with unfractionated heparin at an initial dose of 2000–3000 U and a maintenance dose of 500–1000 U/h. Patients with bleeding tendency were anticoagulated with sodium citrate. For patients with contraindications to sodium citrate, heparin-free dialysis was performed in case of active bleeding, and vascular lines were flushed regularly with normal saline. The pattern of CRRT was the same in all patients.

3. Measures

3.1. Clinical data

The general data of patients in the two groups, including age, body mass index (BMI), Acute Physiology and Chronic Health Evaluation II (APACHEII) score, gender, hypertension, diabetes mellitus, and type of infection, were compared. Laboratory indicators, including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and albumin levels were detected and compared between the two groups.

3.2. Time to assessment of plasma concentrations of polymyxin B

The fasting venous blood of patients was collected before the next dose, at the end of the infusion and after 6 h of administration polymyxin B, and centrifuged at 3000r/min for 10 min. The supernatant was taken and liquid chromatography-mass spectrometry was used to detect the level of plasma concentration of polymyxin B measured before the next administration (C_{min}), peak plasma concentration of polymyxin B measured immediately after end of infusion (C_{max}) and intermediate plasma concentration measured 6 h after administration (midpoint of the dosing interval) ($C_{1/2t}$) in the patients.

3.3. Assessment of polymyxin B blood concentration reached the standard

According to the recommendations of relevant guidelines [9], the normal blood concentration of polymyxin B was specified as 50–100 mg/h/L. The blood concentration of the patient after medication was 50~100 mg/h/L, indicating that the blood concentration was up to the standard, and the blood concentration of the patient after medication was <50 mg/h/L or >100u mg/h/L, indicating that the blood concentration was not up to the standard.

3.4. Evaluation of efficacy

According to the *Technical Guidelines for Clinical Trials of Antimicrobial Agents*, the efficacy of patients was evaluated. Effective indicated that patients achieved clinical resolution and bacterial eradication (confirmed eradication or presumed eradication) at the end-of-treatment visits. Ineffective indicted that patients did not achieve clinical resolution or bacterial eradication (confirmed eradication and/or presumed eradication) at the end-of-treatment visit.

3.5. Assessment of complications

Complications and 28-day mortality were recorded in both groups.

3.6. Statistical methods

Data were analyzed using SPSS 20.0 software. The quantitative data such as age, C_{min}, C_{max}, $C_{1/2t}$ were expressed as $\bar{x} \pm s$ and analyzed by *t*-test. Count data such as gender and diabetes mellitus were expressed as (%) and analyzed by $\chi 2$ test. Correlation between plasma concentration and clinical efficacy was analyzed by Spearman correlation. The predictive value of C_{max} on clinical efficacy was determined based on receiver operating characteristic (ROC) curves. Results were statistically significant when $p < 0.05$.

4. Results

4.1. Comparison of general data of patients in the standard group and the non-standard group

Age, BMI, and APACHE II scores of patients in the non-standard group were higher than these in the standard group ($p < 0.05$, Table 1).

4.2. Multivariate logistic regression analysis of factors affecting the pharmacokinetics of polymyxin B

Multivariate logistic regression analysis showed that both BMI and APACHE II scores were independent risk factors affecting the pharmacokinetics of polymyxin B in patients with severe pulmonary infection ($p < 0.05$, Table 2).

4.3. Comparison of plasma concentrations in the observation group and the control group

The levels of C_{min}, C_{max} and $C_{1/2t}$ in the observation group were lower than these in the control group ($p < 0.001$, Table 3 and Fig. 2A–C).

4.4. Correlation between plasma concentration and efficacy in the two groups

The response rate was 50.00% in the control group and 36.36% in the observation group with no significant difference between the two groups ($p > 0.05$). Spearman correlation analysis showed that the levels of C_{min}, C_{max} and $C_{1/2t}$ were no significant correlation with clinical efficacy in the observation group ($p > 0.05$). The C_{max} level in the control group was significant positive correlation with the clinical efficacy ($r = 0.485$, $p < 0.05$). The ROC curves were plotted to analyze the predictive value of C_{max} on clinical efficacy in the control group. The results showed that AUC was 0.796 (95% CI: 0.627 to 0.964) with a cut-off value of 7.15 μg/ml, a sensitivity of 73.33%, a specificity of 80.00%, and a Youden index of 0.533 (Tables 4 and 5, and Fig. 3).

4.5. Comparison of adverse reactions and 28-day mortality in the observation group and the control group

There was no significant difference in the incidence of skin pigmentation and nephrotoxicity between the two groups ($p > 0.05$), and there was also no significant difference in 28-day mortality between the two groups ($p > 0.05$, Table 6 and Fig. 4).

Table 1
Comparison of general data of patients in the standard group and the non-standard group ($\bar{x} \pm s$, %).

Indexes		The standard group (n = 20)	The non-standard group (n = 15)	t/χ^2	*p*
Age (years)		59.88 ± 5.43	65.26 ± 7.29	2.506	0.017
Gender	Male	12 (60.00)	8 (53.33)	0.156	0.693
	Female	8 (40.00)	7 (46.67)		
BMI value (kg/m^2)		21.05 ± 2.43	25.02 ± 1.88	5.251	<0.001
APACHE II score		20.53 ± 3.16	28.72 ± 2.95	7.804	<0.001
Type of infection	Pulmonary infection	8 (40.00)	10 (66.67)	2.832	0.243
	Bloodstream infection	11 (55.00)	4 (26.67)		
	Other	1 (5.00)	1 (6.67)		
Alanine aminotransferase (U/L)		31.25 ± 9.78	30.26 ± 8.59	0.312	0.757
Aspartate aminotransferase (U/L)		37.52 ± 11.26	40.36 ± 15.67	0.625	0.537
Alkaline phosphatase (U/L)		145.36 ± 41.78	150.87 ± 62.49	0.313	0.757
Albumin (g/L)		32.62 ± 6.47	31.12 ± 5.87	0.706	0.485
CRRT	Yes	5 (25.00)	2 (13.33)	0.729	0.393
	No	15 (75.00)	13 (66.67)		

Table 2
Multivariate logistic regression analysis of factors affecting the pharmacokinetics of polymyxin B.

Indexes	β	*SE*	*Wald* χ^2 Value	*p* value	*OR* value	*95% CI*
Age	0.425	0.373	1.320	0.250	1.533	0.740 to 1.867
BMI	0.457	0.026	6.192	0.018	1.670	1.521 to 2.857
APACHE II scores	0.687	0.259	7.106	0.008	1.988	1.199 to 3.293

Table 3
Comparison of plasma concentrations in the observation group and the control group ($\bar{x} \pm s$).

Group	Number of patients	C_{min} (μg/ml)	C_{max} (μg/ml)	$C_{1/2t}$ (μg/ml)
The control group	28	2.36 ± 0.85	7.26 ± 1.46	3.52 ± 1.02
The observation group	7	0.99 ± 0.23	4.85 ± 1.02	2.16 ± 0.45
t		7.261	6.133	5.632
p		<0.001	<0.001	<0.001

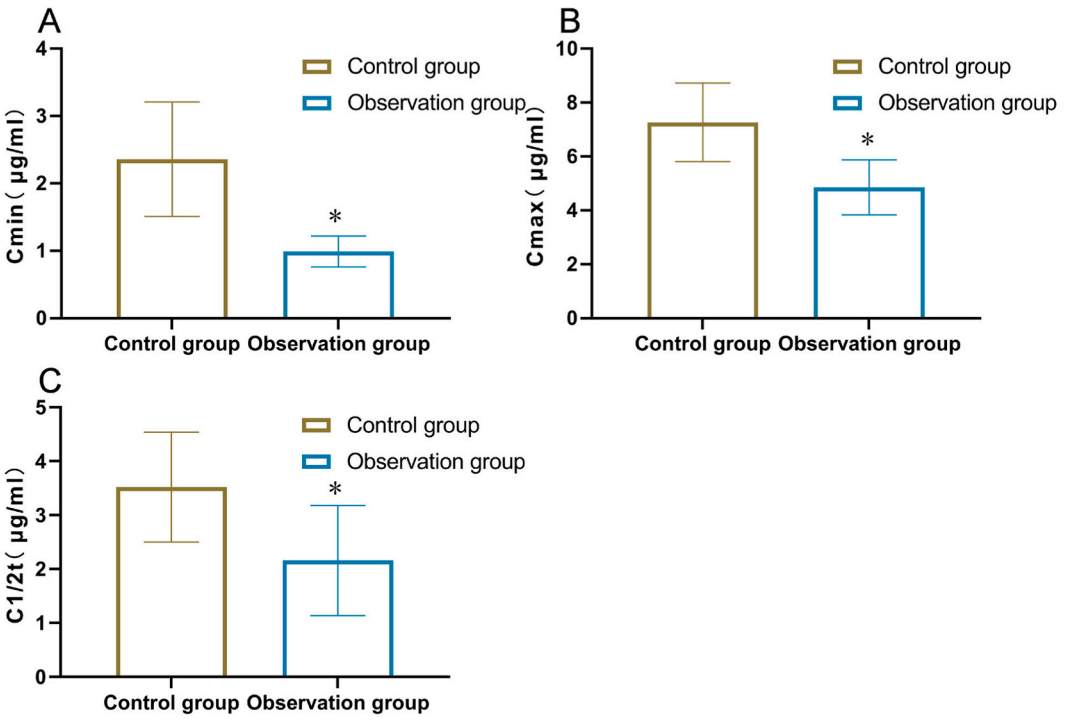

Fig. 2. Plasma concentration in the observation group versus in the control group.
A: The level of C_{min} in the observation group versus the control group. B: The level of C_{max} in the observation group versus the control group. C: The level of $C_{1/2t}$ in the observation group versus the control group. Note: Compared with control group * $p < 0.001$.

Table 4
Correlation between plasma concentration and efficacy in the control group ($\bar{x} \pm s$).

Group		Number of patients	C_{min} (μg/ml)	C_{max} (μg/ml)	$C_{1/2t}$ (μg/ml)
Control group	Effective	14	2.18 ± 0.56	8.16 ± 1.26	3.52 ± 1.56
	Ineffective	14	2.54 ± 0.23	6.36 ± 1.08	3.33 ± 1.74
r			−0.126	0.485	0.095
p			0.498	0.041	0.613

5. Discussion

Severe pulmonary infection is a common acute and critical illness in clinical practice, which is serious and has the characteristics of recurrent episodes and prolonged course of the disease. One study found [10] that the survival rate of patients with pulmonary

Table 5
Correlation between plasma concentration and efficacy in the observation group ($\bar{x} \pm s$).

Group		Number of patients	C_{min} (μg/ml)	C_{max} (μg/ml)	$C_{1/2t}$ (μg/ml)
Observation group	Effective	3	0.87 ± 0.39	3.96 ± 1.75	1.84 ± 0.96
	Ineffective	4	1.06 ± 0.74	5.36 ± 2.06	2.34 ± 1.45
r			0.076	−0.356	−0.251
p			0.912	0.349	0.541

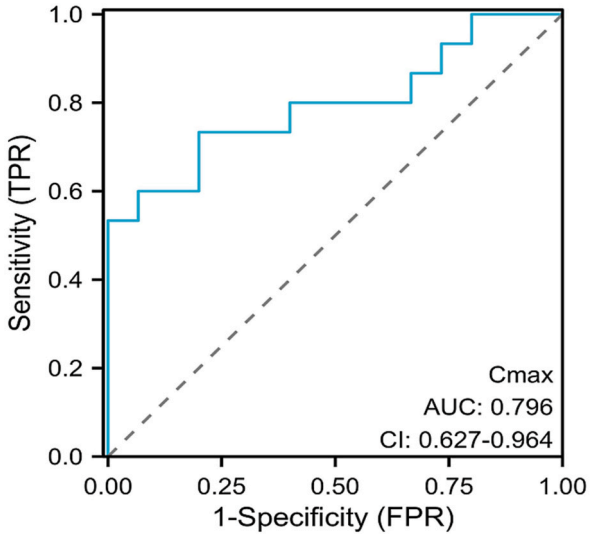

Fig. 3. ROC curve for predicting clinical efficacy of polymyxin B C_{max} in the control group.

Table 6
Comparison of adverse reactions and 28-day mortality in the observation group and the control group.

Group	Number of patients	Skin pigmentation	Nephrotoxicity	28-day mortality
The control group	28	3 (10.71)	6 (21.43)	8 (28.57)
The observation group	7	2 (28.57)	1 (14.29)	4 (57.14)
χ^2		1.784	0.179	2.029
p		0.182	0.673	0.154

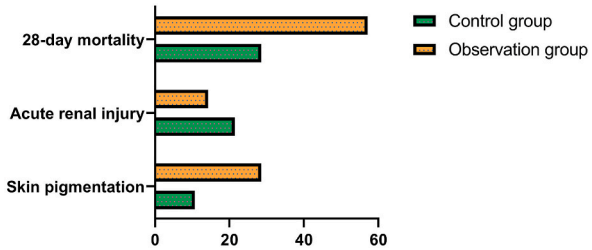

Fig. 4. Comparison of adverse reactions and 28-day mortality in the observation group and the control group.

infection was increased by about 40% with early diagnosis and treatment. Therefore, early diagnosis and accurate treatment of pulmonary infection are crucial to improve the cure rate. Polymyxin B is widely used in the infections of gram-negative bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa*, and *Acinetobacter*. However, the therapeutic effect and toxic side effects are closely related to the blood concentration, thus it is gradually replaced by other antibacterial drugs because of its narrow antibacterial spectrum. With the abuse of antibiotics in recent years, the incidence of multi-drug resistant gram-negative bacterial infections has been increasing year by year, and polymyxin B has become a common drug for the clinical treatment of severe pulmonary infections caused by Gram-negative bacteria. At the same time, the study believes that regular monitoring of polymyxin B plasma concentrations and timely adjustment can contribute to improve efficacy and reduce toxicity and side effects [11].

This study showed that both BMI and APACHE II score were independent risk factors affecting the pharmacokinetics of polymyxin B in patients with severe pulmonary infection. Obese patients have more fat. The metabolites of polymyxin B are fat-soluble, and the apparent volume of distribution in obese patients is large, resulting in low blood concentrations. Therefore, for obese patients, clinicians should pay attention to appropriately increasing the dose of polymyxin B in order to obtain a more ideal treatment effect. Higher APACHE II score corresponds to more severe disease. Liver and kidney function decline, drug metabolism and excretion rate slowed down, and clearance half-life is significantly prolonged, which may lead to the accumulation of polymyxin B in the body, so severe patients are recommended by the Infectious Diseases Society of America to need polymyxin B blood concentration monitoring [12]. Hemodialysis is an important mean to filter the blood and remove wastes, toxins and extra fluid. In addition to hemodialysis, CRRT is also a treatment option for infectious diseases such as sepsis. It was reported that CRRT was better tolerated in hemodynamically unstable patients and provided better renal recovery [13]. However, in patients receiving CRRT, there was a great variability in antibiotic pharmacokinetics in the body. CRRT can remove water and metabolic waste products from the body through extracorporeal bypass, reduce the burden on the body's kidneys, and improve the immune function of patients by removing inflammatory mediators. It is hemodynamically stable, which can help to quickly control the changes in severe pulmonary infection [14]. However, CRRT also reduces the plasma concentration of antibiotics (e.g., polymyxin B) and interferes with the normal metabolism of antimicrobials (e.g., polymyxin B) [15,16]. The previous study suggested that there is no need to adjust the dose of polymyxin B in patients with severe pulmonary infections during CRRT [17]. In this study, the levels of C_{min}, C_{max} and $C_{1/2t}$ in the observation group were significantly lower than those in the control group. The response rate was 50.00% in the control group and 36.36% in the observation group with no significant difference, suggesting that CRRT indeed lowered the plasma concentration of polymyxin B in patients. For patients receiving CRRT, changes in polymyxin B plasma concentration should be regularly monitored and the dose of polymyxin B should be increased on a case-by-case basis. However, CRRT had less effect on the efficacy of polymyxin B, which might be the result of disease progression and patient' s physical status.

Antibiotics are effective treatment options for pulmonary infection. However, in recent years, the wide application of antibiotics in clinical practice and poor control of infection within hospitals contribute to a global problem of bacterial resistance, with an increasing rate year by year. In particular, carbapenem-resistant gram-negative bacteria have a high resistance to conventional antibiotics, significantly increasing the difficulty of clinical treatment [18]. Polymyxin B is a concentration-dependent antibacterial. Low blood concentrations of polymyxin B can easily induce drug resistance in gram-negative bacteria, while high blood concentrations can cause nephrotoxicity, skin melanin and other toxic side effects. Therefore, guidelines have suggested that steady-state plasma concentration of polymyxin B should be maintained at 2–4 mg/L [19,20]. However, this recommendation was based on the results from mouse model studies rather than clinical trials. The threshold of efficacy could be determined based on the correlation between plasma concentration and clinical efficacy, and thus guiding the treatment plan and improving the efficacy. By analyzing the relationship between blood drug concentration and clinical efficacy, the determination of efficacy threshold is helpful to guide the treatment plan and improve the efficacy. In this study, the levels of C_{min}, C_{max} and $C_{1/2t}$ in the observation group were no significant correlation with clinical efficacy. The C_{max} level in the control group was significant positive correlation with clinical efficacy, and 7.15 μg/ml was the threshold concentration of polymyxin B that was clinically effective, indicating that there was a correlation between C_{max} and clinical efficacy without CRRT. Further study will determine the clinical therapeutic threshold concentration and reduce the difficulty of clinical operation. In addition, polymyxin B can be cleared by both renal and extrarenal pathways, and it is currently believed that the proportion of renal clearance is relatively high. At the same time, the tissue diffusion of polymyxin B is poor, so it may cause toxic side effects such as nephrotoxicity and tubular damage [20,21]. In this study, there was no significant difference in creatinine clearance before and after administration between the two groups, and there was no difference in adverse reactions and 28-day mortality between the two groups, indicating that the dose of polymyxin B in this experiment had little effect on the renal function of the patients, did not increase the risk of death, and was relatively safe.

In summary, CRRT reduced the plasma concentrations of polymyxin B. There is a certain correlation between the C_{max} level and the clinical efficacy of patients with severe pulmonary infection who have not been treated with CRRT. Monitoring the plasma concentration of polymyxin B in patients is helpful for timely adjustment of clinical medication, which can help achieve effective plasma concentrations and reduce toxic side effects. However, due to the small number of samples in this experiment, there might be some errors in the experimental results. In addition, the study time of this experiment was relatively short, and the effect of CRRT modes on the plasma concentration of polymyxin B did not be analyzed. In the future, we will expand the experimental subjects and research time and conduct further in-depth investigations.

Ethics approval and consent to participate

This study was approved by The Ethics Committee of The Third People's Hospital of Chengdu (Approval number: 2021S-15). Written Informed Consent was obtained from participants for the participation in the study and all methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

The patients participating in the study all agree to publish the research results.

Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

Not applicable.

CRediT authorship contribution statement

Xi Wang: Writing – original draft, Methodology, Investigation, Data curation. **Mingming Zhou:** Visualization, Software, Methodology. **Xiyu Wang:** Visualization, Validation, Methodology. **Lian Liu:** Visualization, Project administration, Conceptualization. **Chuan Zhang:** Writing – review & editing, Software, Methodology, Investigation, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e27558.

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