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Original Article

Effects of sequential blood purification on the organ function and lethality in patients with paraquat-induced multiple organ dysfunction syndrome

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Abstract: Objective: To explore the efficacy of sequential blood purification in paraquat (PQ) poisoning-induced multiple organ dysfunction syndrome (MODS). Methods: Forty-six patients with MODS caused by PQ poisoning admitted to our hospital during January 2016-December 2020 were retrospectively enrolled. The patients were allocated into the experimental group (n = 20) and the control group (n = 26) in accordance with the different treatment methods of blood purification. The experimental group was given sequential blood purification, and the control group was given separate blood purification. The two groups were compared in terms of blood biochemical indices, inflammatory factor levels, level of organ injury and treatment efficiency. Results: The blood biochemical indices and inflammatory factor levels after treatment were noticeably reduced in both groups ($P < 0.05$), and the experimental group exhibited lower alanine aminotransferase, MB isoenzyme of creatine kinase, creatinine and blood urea nitrogen than the control group at 3 and 5 days after treatment ($P < 0.05$). The experimental group exhibited remarkably lower aspartate aminotransferase, lactate dehydrogenase, interleukin-6 and tumor necrosis factor-α levels, and noticeably higher interleukin-10 levels than the control group at 5 days after treatment ($P < 0.05$). After treatment, the experimental group showed remarkably lower overall organ damage rate (10%) than the control group (58.69%). After treatment, the two groups exhibited remarkably lower disease severity than that before treatment ($P < 0.05$). At 5 days after treatment, the experimental group showed remarkably lower Acute Physiology and Chronic Health Evaluation II score than the control group ($P < 0.05$). The experimental group showed noticeably shorter duration of mechanical ventilation, length of coma, intensive care unit stay and hospital stay than the control group after treatment ($P < 0.05$). The experimental group showed a remarkably higher overall efficiency of treatment (90%) than the control group (76.92%). Conclusion: Compared with blood purification therapy alone, sequential blood purification therapy can improve the indices of liver function and coma status, suppress the inflammatory response, reduce the APACHE II score, and shorten the overall duration of treatment of patients with PQ poisoning-induced MODS.

Keywords: Paraquat, sequential blood purification, multiple organ dysfunction syndrome

Introduction

Paraquat (PQ), chemically known as 1,1'-Dimethyl-4,4'-bipyridinium dichloride hydrate, is now commonly used in agriculture and horticulture due to its high herbicidal efficacy and low cost [1]. PQ is a highly toxic pesticide with low lethal dose. About 300,000 people lose their lives due to PQ poisoning each year, and the absolute number of poisoning deaths ranks top among all pesticide-related deaths [2, 3].

PQ can enter the human body through the digestive tract, respiratory tract, and skin or mucous membrane contact, and clinically, it is mostly poisoned by oral intake. After entering the human body, PQ will rapidly invade all tissues and organs, primarily the lung, which actively absorbs PQ, and the concentration of PQ in the lung is 10-90 times higher than that in other organs [4]. Vale et al. found that disease severity of patients with PQ poisoning was positively correlated with the intake of PQ, and when the oral dose was greater than 40 mg/kg, patients would rapidly develop multiple organ dysfunction syndrome (MODS), and in severe cases, multiple organ failure may lead to death [5, 6].

Currently, PQ poisoning lacks specific antidotes. PQ poisoning is generally believed to be related to free radicals and oxidative stress, and can be treated with antioxidant drugs to scavenge oxygen free radicals or through gastric lavage and diuretics to accelerate the excretion of toxic substances [7]. It has been found that the toxicity intensity of PQ in humans has positive correlation with plasma PQ concentration, with the higher plasma PQ concentration representing the stronger toxicity and the more severe tissue damage in patients [8]. Therefore, reducing the concentration of PQ in plasma is very important for the rescue of patients with PQ poisoning.

Since 1955, when Schreiner et al. first reported the use of hemodialysis (HD) in treating poisoned patients, HD has become a key tool for acute poisoning. HD and hemoperfusion (HP) are common methods of blood purification. Sequential blood purification is a new blood purification technology, which can remove toxic substances from the body of poisoned patients, maintain the internal environment in a stable state, decrease the inflammatory response, and protect organ function [9, 10].

In this study, we compared the differences in blood biochemical indices, inflammatory factor levels, organ damage, and treatment efficiency between separate blood purification and sequential blood purification in patients with PQ poisoning-induced MODS, thereby providing a theoretical basis for promoting the therapeutic efficacy in patients with PQ poisoning.

Materials and methods

General data

Forty-six patients with PQ poisoning-induced MODS admitted to the emergency department of our hospital between January 2016 and December 2020 were retrospectively enrolled and analyzed. The patients were allocated into the experimental group (n = 20) and the control group (n = 26) in accordance with different treatment methods of blood purification selected by patients. This study had been approved by the Ethics Committee of Hanzhong Center Hospital (Approval No. PJ2021-0786).

Inclusion criteria: (1) patients with an age of 18-75 years; (2) patients with oral PQ poisoning; (3) patients who received blood purification treatment within 3 h after admission; (4) patients whose family members provided informed consent.

Exclusion criteria: (1) patients with combined multi-substance poisoning; (2) patients with history of severe organ disease; (3) patients whose family members gave up treatment within a short time; (4) patients with incomplete treatment data.

Intervention method

Patients in both groups received conventional resuscitation measures such as oxygenation supply, gastric lavage and catheterization according to their own conditions.

On the basis of conventional resuscitation measures, the control group was administered HP treatment at a blood flow rate of 150-200 mL/min for 2 h each time. Patients were given systemic heparin anticoagulation during HP treatment with 100 mg 12500 U low molecular weight heparin (Low Molecular Weight Heparin Sodium Gel, Approval No. H20040409) dissolved in 500 mL normal saline, and the activated clotting time (ACT) index of patients was monitored. The initial load and additional dose were determined according to the ACT monitoring value.

The experimental group was given continuous renal replacement therapy (CRRT) in combination with the therapy given in the control group. The initial dose was 100 mL/min and gradually increased to the maximum dose of 180 mL/min, with a replacement rate of 2000 mL/h and a dialysis fluid rate of 1000 mL/h. Patients continued the treatment course for 12-24 h each time. For patients without bleeding prone, heparin was administrated to maintain the level of ACT at 160-180 s, and the dose of heparin was adjusted according to the changes of ACT. Patients prone to bleeding were treated with heparin-free anticoagulation, and the tube was rinsed once every hour to observe the coagulation.

Outcome measurement

Primary indicators

Blood biochemical indices: Five milliliters of fasting venous blood was drawn from patients

before treatment and at day 3 and 5 after treatment. Serum was obtained after centrifugation, and biochemical indices including alanine aminotransferase (ALT), aspartate aminotransferase (AST), MB isoenzyme of creatine kinase (CK-MB), lactate dehydrogenase (LDH), creatinine (Cr), and blood urea nitrogen (BUN) were measured using a fully automatic biochemical analyzer (Myriad, BS-240).

Degree of organ damage: Patients underwent computed tomography (CT) lung screening before treatment and at day 5 after treatment. The degree of organ damage was assessed by observing the thickening of lung texture, dotted shadow and pleural effusion.

Clinical treatment: The two groups were compared in terms of duration of mechanical ventilation, length of coma, intensive care unit (ICU) stay and hospital stay during treatment.

Secondary indicators

Evaluation of severity of illness: The Acute Physiology and Chronic Health Evaluation II (APACHE II) scale was used to evaluate the patient's condition before treatment and at day 5 after treatment, which is currently the most commonly used scale for severity of illness. The scoring system includes three domains, namely the scores of acute physiology, age, and chronic health status, with higher scores representing more severe condition [11].

Inflammatory factors: Five milliliters of fasting peripheral venous blood was drawn from patients before treatment and at day 5 after treatment. Serum was collected after static centrifugation, and interleukin-6 (IL-6), interleukin-10 (IL-10), and tumor necrosis factor-α (TNF-α) levels were measured by enzyme-linked immunoassay.

Evaluation of therapeutic efficacy: The concentration of PQ in the blood of the patients after treatment was measured, and the adverse reactions were observed to evaluate the therapeutic efficacy.

After treatment, if PQ was effectively removed from the patient's body without adverse reactions, the therapeutic efficacy was rated as markedly effective; if the patient's vital signs were basically stable after treatment, but still needed to be monitored, the therapeutic efficacy was rated as effective; if the patient died after treatment, the therapeutic efficacy was rated as ineffective.

The overall effective rate = markedly effective rate + effective rate.

Statistical methods

The data were statistically analyzed using SPSS 22.0. The measurement data were expressed as mean ± standard deviation ($\bar{x}\pm$sd). Independent-sample t test was conducted for measurement data comparison between the two groups. One-way analysis of variance (ANOVA) followed with least significant difference (LSD) analysis was adopted for comparison of measurement data at different time points. The counting data were expressed as n (%) and compared using χ^2 test. $P < 0.05$ denoted a significant difference.

Results

Comparison of baseline data

No significant difference was found between the two groups in the aspect of gender, age, degree of PQ poisoning, and time from intoxication to the start of hemodilution ($P > 0.05$) (**Table 1**).

Analysis of blood biochemical indices

Before treatment, both groups showed no significant difference in blood biochemical indices ($P > 0.05$). After treatment, both groups showed remarkably lower blood biochemical indices than those before treatment ($P < 0.05$), and the indices were gradually decreased over time. The experimental group showed remarkably lower levels of ALT, CK-MB, Cr and BUN than those of the control group at day 3 and 5 after treatment, and remarkably lower levels of AST and LDH than those of the control group at day 5 after treatment ($P < 0.05$) (**Figure 1**).

Comparison of inflammatory factor levels

The two groups showed no significant difference in levels of each inflammatory factor before treatment ($P > 0.05$). After treatment, the levels of IL-6 and TNF-α factor significantly decreased while the level of IL-10 significantly increased in both groups than those before

Table 1. Comparison of baseline data ($\bar{x}$±sd)/[n (%)]

Baseline data	Control group (n=26)	Experimental group (n=20)	t/X^2	*P*
Gender			0.253	0.615
Male	15	13		
Female	11	7		
Mean age (Y)	53.26±12.57	54.38±13.10	0.073	0.925
PQ poisoning level			0.552	0.759
Mild type	3	2		
Moderate-severe	6	3		
Explosive	17	15		
Time from poisoning to the start of blood purification (h)	34.42±10.46	35.09±14.67	0.192	0.893

PQ: paraquat.

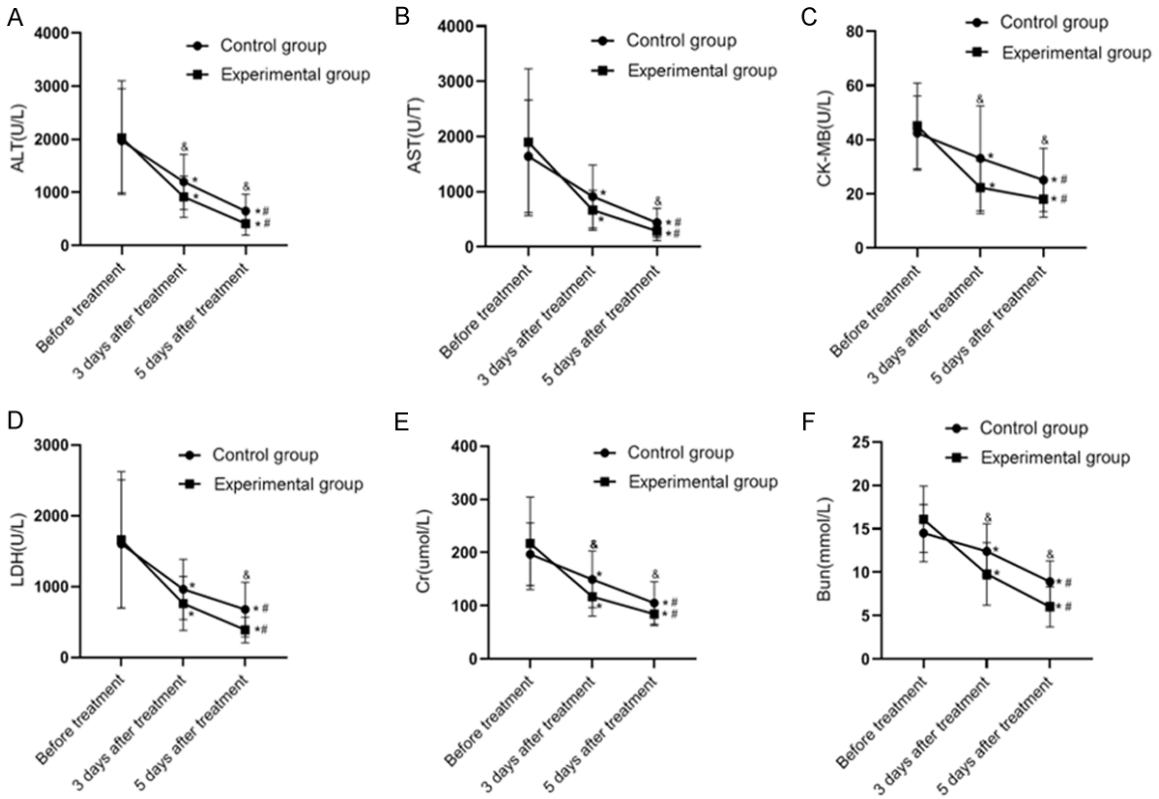

Figure 1. Comparison of blood biochemical indices. A: ALT; B: AST; C: CK-MB; D: LDH; E: Cr; F: BUN. ALT: alanine aminotransferase, AST: aspartate aminotransferase, CK-MB: MB isoenzyme of creatine kinase, LDH: lactate dehydrogenase, Cr: creatinine, BUN: blood urea nitrogen. *Compared with before treatment, $P < 0.05$; &, compared with the control group, $P < 0.05$; #, compared with 3 days after treatment, $P < 0.05$.

treatment ($P < 0.05$). The experimental group exhibited remarkably lower levels of IL-6 and TNF-α and remarkably higher levels of IL-10 than those of the control group ($P < 0.05$) (**Figure 2**).

Comparison of the degree of organ damage

Among patients of the experimental group, 5% showed lung texture thickening, 5% showed pleural effusion, and the rest patients had no

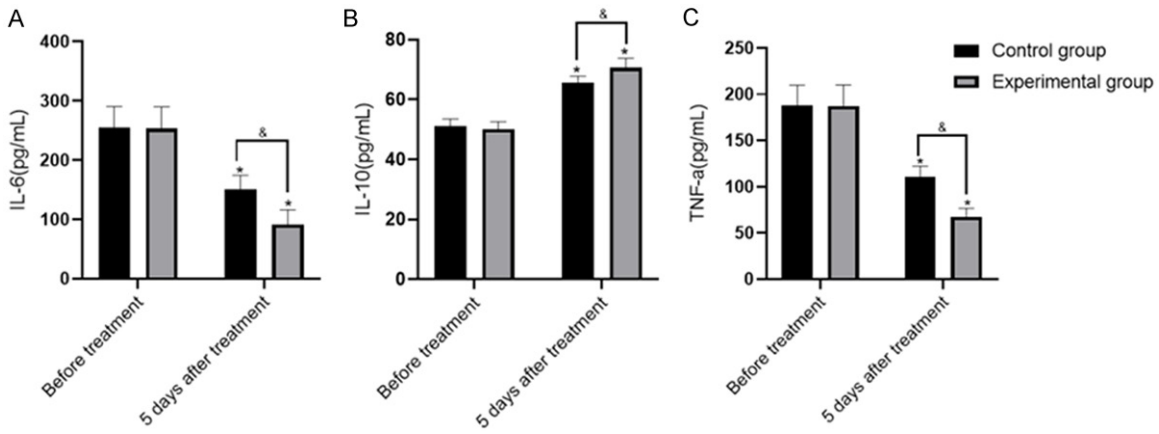

Figure 2. Comparison of inflammatory factor levels. A: IL-6; B: IL-10; C: TNF-α. IL-6: interleukin-6, IL-10: interleukin-10, TNF-α: tumor necrosis factor-α. *Compared with before treatment, $P < 0.05$; &, compared with the control group, $P < 0.05$.

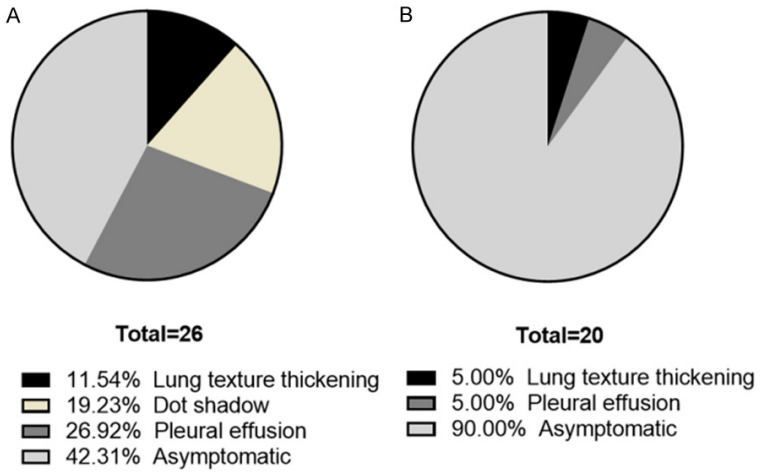

Figure 3. Comparison of the degree of organ damage. A: Control group; B: Experimental group.

obvious organ damage, with the overall organ damage rate of 10%. In the control group, 11.54% showed lung texture thickening, 19.23% showed dotted shadow, 26.92% showed pleural effusion, and the rest patients had no obvious organ damage, with the overall organ damage rate of 58.69% (**Figure 3**).

Comparison of severity of illness

Both groups showed no significant difference in APACHE II scores before treatment ($P > 0.05$). After treatment, both groups exhibited significantly lower APACHE II scores than those before treatment ($P < 0.05$). With the extension of treatment time, APACHE II scores were gradually decreased, and were lower in the experiment group than those in the control group. At day 5 after treatment, the experimental group showed remarkably lower APACHE II scores than the control group ($P < 0.05$) (**Table 2**).

Comparison of clinical treatment

The experimental group exhibited remarkably shorter duration of mechanical ventilation, length of coma, ICU stay and hospital stay than those in the control group ($P < 0.05$) (**Figure 4**).

Comparison of the therapeutic effect

The experimental group obtained an overall effective rate of 90%, which was significantly higher than 76.92% of the control group (**Figure 5**).

Discussion

Blood purification is a treatment that removes toxic substances from the patients' blood through purification devices to purify the blood and support organ functions, and blood purification can maintain the stability of the patients' internal environment, which is of importance in rescue and treatment of patients with

Table 2. Comparison of APACHE II scores

Group	Before treatment	3 days after treatment	5 days after treatment
Control group (n=26)	18.63±3.02	14.96±2.98*	13.95±4.03*
Experimental group (n=20)	19.35±2.27	14.52±2.98*	11.23±4.26*,&,#

APACHE II: Acute Physiology and Chronic Health Evaluation II. *, compared with before treatment, $P < 0.05$; &, compared with the control group, $P < 0.05$; #, compared with 3 days after treatment, $P < 0.05$.

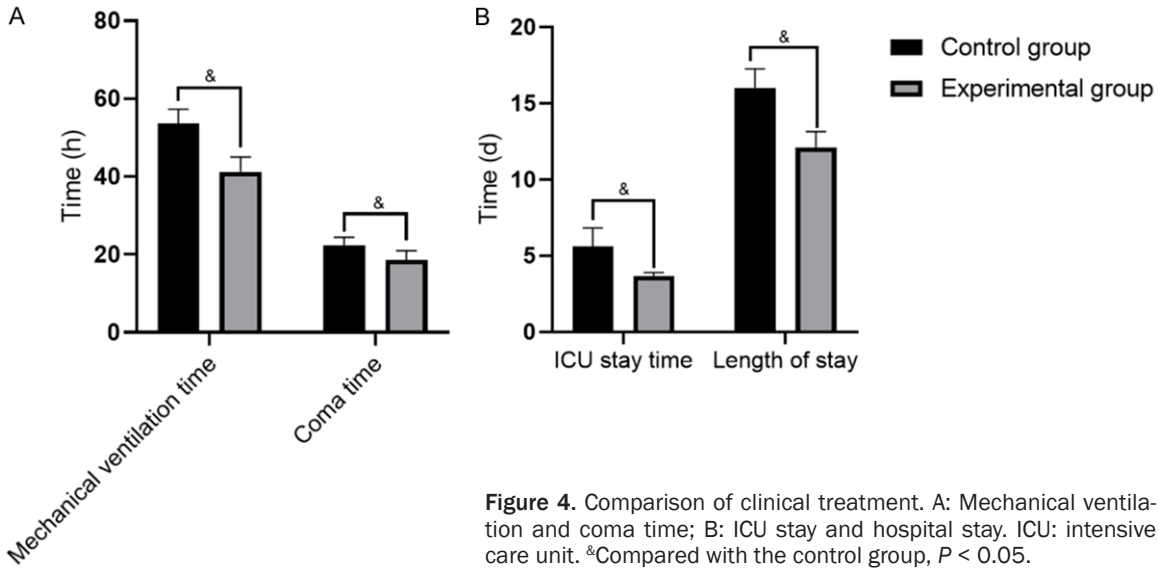

Figure 4. Comparison of clinical treatment. A: Mechanical ventilation and coma time; B: ICU stay and hospital stay. ICU: intensive care unit. &Compared with the control group, $P < 0.05$.

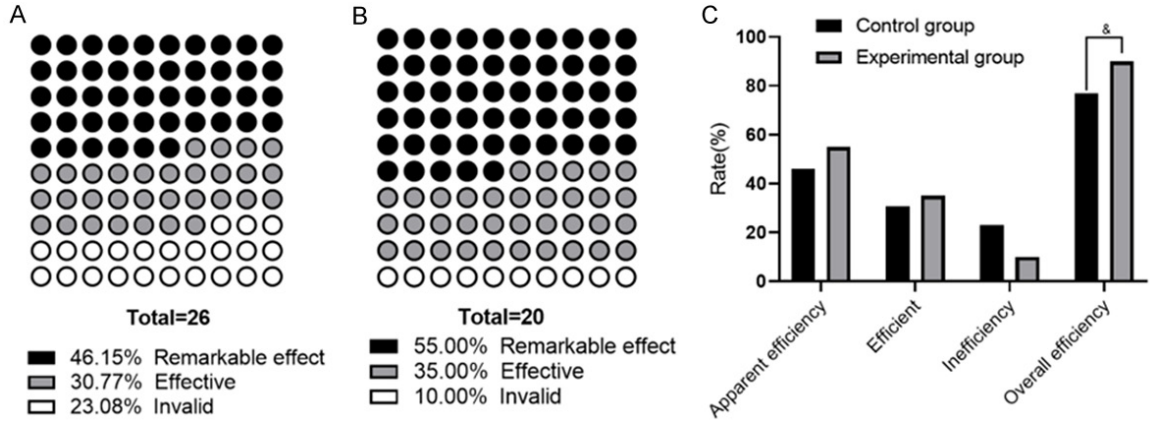

Figure 5. Comparison of the efficacy of patients. A: Control group; B: Experimental group; C: Effective rate. &Compared with the control group, $P < 0.05$.

acute poisoning [12]. Different blood purification methods have their own advantages. HP can effectively remove small-molecule toxicants with high lipid solubility and protein binding abilities by extracting the patient's blood from the body and through physical adsorption purification. However, HP cannot correct the disorders of water-electrolyte and acid-base balance [13, 14]. HD uses dialysis membranes to remove toxicants by diffusion and convection. Although HD can decrease the Cr and BUN levels of patients and correct water-electrolyte and acid-base balance disorders, it cannot effectively remove toxicants of larger molecular weights due to the reduced permeability of dialysis membranes [15]. Plasma exchange (PE) separates blood components through a plasma separator, removes abnor-

mal plasma, and transfuses the same amount of fresh plasma or protein replacement fluid back into the body, which is suitable for removing toxicants that are not easily removed by HD and HP [16]. CRRT is a new treatment method for continuous and slow removal of toxicants, which is slow but can be performed continuously, and has a good effect on maintaining internal environment stability and organ function in the later stages of the poisoned patients [17]. It was shown that different blood purification methods can achieve various therapeutic efficacy according to the specific conditions and stages of poisoned patients [18, 19].

In this study, it was found that ALT, AST, LDH, CK-MB, Cr and BUN of patients in both groups were gradually decreased, and the experimental group showed lower biochemical indices than the control group, suggesting that patients in the experimental group had lower level of liver injury than that in the control group. The reason may be that HP can rapidly reduce the plasma PQ concentration of patients; while coupled with the continuous removal of PQ by CRRT, it can more effectively remove PQ and reduce the degree of damage to the organ function [20]. Gil et al. investigated the correlation between the plasma PQ level and the outcome in 375 patients with PQ poisoning, and found that CRRT could make up for the shortcomings of HP, reduce the duration of treatment, remove the toxins more effectively, and reduce the incidence of PQ concentration rebound [21]. Dinis-Oliveira et al. conducted a multicenter retrospective study on patients with PQ poisoning, and the findings showed that HP combined with CRRT could reduce PQ concentrations, better protect organ function, and minimize the risk of MODS [22]. The CT examination of this study suggested that the experimental group showed remarkably lower overall organ damage rate than that in the control group. After treatment, the experimental group showed remarkably lower IL-6 and TNF-α levels as well as remarkably higher IL-10 levels than those in the control group at day 5 after treatment. This may be due to the fact that inflammation is involved in the pathogenesis of PQ toxicity, and the release of a variety of inflammatory factors disrupts the inflammatory and anti-inflammatory responses as well as aggravates the dysfunction of immune system and organs of the body. Blood purification reduced levels of inflammatory factors, cleared inflammatory transmitters from the blood and maintained internal environment stability of the body [23, 24]. APACHE II scores showed that the disease severity of both groups were remarkably lower after treatment than those before treatment; at day 5 after treatment, the experimental group showed remarkably lower APACHE II scores than the control group. The experimental group exhibited remarkably shorter duration of mechanical ventilation, length of coma, ICU stay and hospital stay and remarkably higher overall efficiency of treatment than those in the control group.

In conclusion, sequential blood purification was better than single blood purification in treating patients with PQ poisoning-induced MODS, which finding is similar to that of Isfahani et al. by a meta-analysis of 12 relevant papers [25]. Sequential blood purification can give full play to the advantages of different blood purification methods, which can efficiently remove PQ from patients, suppress inflammatory reactions, maintain the stability of the body's internal environment, improve patients' liver and kidney function as well as the overall efficiency of treatment, cut down treatment time, and thus improve prognosis of patients, which has clinical significance for promotion. The deficiency of the study is that the effect of blood purification at different times and frequencies was not systematically analyzed. In the future studies, the sample size will be increased to obtain more accurate experimental conclusions.

Disclosure of conflict of interest

None.

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