

Original Article

Effects of early repeated hemoperfusion combined with hemodialysis on the prognosis of patients with paraquat poisoning

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Abstract: Objective: To investigate the effect of early, repeated hemoperfusion in conjunction with hemodialysis on the health status, blood-gas indices, and prognosis of patients with paraquat (PQ) poisoning. Methods: In this retrospective study, clinical data of 149 PQ-poisoned patients treated at Xianyang First People's Hospital between January 2019 and January 2022 were analysed. Sixty-two patients who received conventional treatment coupled with early, repeated hemoperfusion were designated as the control group. The remaining 87 patients, who were subjected to additional hemodialysis on the basis of the control group, were designated in the experimental group. A comparison was made between the two groups regarding the changes in liver function, renal function, and blood-gas indices before and after the treatment. Three-month survival outcomes of both groups were analyzed using Cox regression, with survival curves drawn for different prognostic factors. Results: The experimental group exhibited significantly lower levels of indirect bilirubin (IBiL) and glutamic-pyruvic transaminase (ALT) after the treatment compared to the control group (all $P < 0.05$), as well as markedly lower levels of total bilirubin (TBil), direct bilirubin (DBil), glutamic-oxaloacetic transaminase (AST), alkaline phosphatase (ALP), urea nitrogen (BUN), and creatinine (Cr) (all $P < 0.01$). The experimental group also demonstrated significantly improved arterial partial pressure of oxygen (PaO_2) and $\text{PaO}_2/\text{inspired oxygen (FIO}_2)$ ratios, along with reduced arterial carbon dioxide partial pressure (PaCO_2) after the treatment (all $P < 0.05$). Moreover, a significantly higher three-month survival rate was observed in the experimental group compared to the control group ($P < 0.001$). According to Cox regression analysis, blood purification mode, age, urine PQ concentration upon admission, the timing of initial gastric lavage and bowel cleanse, and the timing of initial blood purification were identified as independent factors affecting the patients' 90-day prognosis. Conclusion: Early, repeated hemoperfusion coupled with hemodialysis significantly improves the blood-gas indices and liver and kidney function in patients with PQ poisoning, while also extending their short-term survival.

Keywords: Early repeated hemoperfusion, hemodialysis, paraquat poisoning, blood gas index, prognosis

Introduction

Paraquat (PQ), commercially known as Gramoxone, is a non-selective contact herbicide widely favored by agricultural and landscape workers due to its high weed control efficiency, cost-effectiveness, and non-polluting properties [1]. However, the extensive usage of PQ has led to an increased incidence of poisoning. In fact, PQ poisoning ranks second among all types of pesticide poisoning, with the absolute number of PQ poisoning-related deaths being the highest [2]. PQ's extreme toxicity to humans and livestock can be lethal, even in small quantities, with most patients succumbing to oral poisoning [3]. The poison can infiltrate the

human body via various channels, including skin/mucosal contact, respiratory inhalation, and gastrointestinal absorption. Once inside, PQ inflicts damage on many vital organs, with the lungs being the primary target [4]. Characterized by acute lung injury and irreversible pulmonary fibrosis, PQ poisoning progresses rapidly, often resulting in systemic multi-organ failure and a high mortality rate [5, 6]. Despite regulations banning the production and sale of PQ aqueous agents in China, PQ poisoning remains a common type of pesticide poisoning in emergency departments due to factors such as private hoarding, lax corporate management, and a lack of public safety awareness [7]. Currently, no specific antidotes or effective

Enhancing PQ poisoning survival with early repeated hemoperfusion

treatment measures exist for PQ poisoning, resulting in a persistently high clinical mortality rate.

Contrary to organophosphates or other toxic poisons, no specific treatment method for PQ poisoning is available at this stage [8]. Current clinical treatments mainly include gastric lavage, bowel cleanse, blood purification, and the administration of hormones, immunosuppressants, and antioxidants [9]. Of these, blood purification treatment is the most critical. Early, repeated hemoperfusion following PQ poisoning can reduce toxin accumulation in the body and enhance the therapeutic outcome [10]. However, hemoperfusion can only eliminate macromolecular toxins, failing to remove small molecular toxins and inflammatory factors in the body, and unable to maintain the body's internal environmental balance. Hemodialysis compensates for these shortcomings. Clinical research has validated that early, repeated hemoperfusion combined with hemodialysis significantly improves patients' liver and kidney function and increases the survival rate compared to early, repeated hemoperfusion alone [11]. However, there is an ongoing debate about the adoption of early combined hemodialysis, as experts suggest hemodialysis should only be considered when renal function is compromised.

Currently, the treatment of paraquat poisoning primarily involves gastric lavage to remove unabsorbed poison and administration of activated charcoal to limit further absorption. Antioxidants such as N-acetylcysteine and immunosuppressive therapy are also utilized in attempts to limit the pulmonary fibrosis which often results in mortality. Despite these interventions, the prognosis remains poor, with a high mortality rate. This emphasizes the need for innovative approaches and therapies for paraquat poisoning. Our study explores effects of early repeated hemoperfusion combined with hemodialysis on prognosis in patients with paraquat poisoning and holds significant clinical implications by potentially improving both the survival rates and quality of life in patients suffering from paraquat poisoning.

Materials and methods

Ethical statement

This study was performed with permission from the Medical Ethics Committee of Xianyang First People's Hospital.

Patient sources

The data of 184 patients with PQ poisoning treated in Xianyang First People's Hospital between January 2019 and January 2022 were retrospectively studied.

Inclusion and exclusion criteria

Inclusion criteria: patients with positive urine PQ test result; patients whose PQ poisoning was oral PQ poisoning [12] (were restricted to cases of oral paraquat poisoning due to the uniformity of exposure, the typically severe clinical course, and its epidemiological relevance as the most common route of paraquat poisoning); patients who were newly diagnosed in Xianyang First People's Hospital; patients who received blood purification treatment; patients with complete case data.

Exclusion criteria: patients with a history of liver or renal insufficiency; patients comorbid with other drug poisoning; patient with hematological diseases; patients during pregnancy or lactation; patients who did not receive individualized treatment or gave up treatment due to various reasons after admission; patients comorbid with infectious diseases or malignant tumors; patients comorbid with autoimmune diseases.

Sample screening

According to the inclusion and exclusion criteria, 149 eligible patients were screened out. The patients were grouped according to different therapeutic regimen. Among them, 62 patients who received routine treatment and early repeated hemoperfusion were assigned to the control group, and the other 87 patients who received hemodialysis additionally based on treatment in the control group were assigned to the experimental group.

Therapeutic regimen

Each patient was given a urine PQ test at admission, and the result was positive. In addition to general treatment, the patient received blood purification treatment. General treatment included the following treatments: 1. Poison removal: Patients without contraindications should be given gastric lavage immediately. A 2% sodium bicarbonate solution (national medicine standard H37021234, Shandong Shenglu Pharmaceutical Co., Ltd.)

Enhancing PQ poisoning survival with early repeated hemoperfusion

was adopted for gastric lavage until the gastric lavage fluid was colorless and odorless, which generally took 3-5 L. Meantime, bowel cleanse was carried out. Oral polyethylene glycol electrolytes powder II (Guoyao Zhanzi H20030827, Shenzhen Wanhe Pharmaceutical Co., Ltd.) or 20% mannitol (Guoyao Zhanzi H20184101, Hubei Tiansheng Pharmaceutical Co., Ltd.), added with 50 g medicinal carbon powder and 2 L clear water, was adopted for bowel cleanse.

2. Drug therapy: Glucocorticoid methylprednisolone (Sinopharmaceutical H20040844, Sino-pharmaceutical Group Rongsheng Pharmaceutical Co., Ltd.) was given intravenously at "0.5 g QD" for 3-5 days (adjusted according to the patient's condition). Thalidomide (national drug standard H32026130, Changzhou Pharmaceutical Factory Co., Ltd.) was used at "50mg Tid" to alleviate lung injury. Vitamin C (National Pharmaceutical Standard H20043-274, Shanxi Pude Pharmaceutical Co., Ltd.), and N-acetylcysteine (National Pharmaceutical Criterion H20051788, Hangzhou Minsheng Pharmaceutical Co., Ltd.) was given through intravenous drip and vitamin E (National Pharmaceutical Criterion H32024177, Nanjing Sea Whale Pharmaceutical Co., Ltd.) was orally administrated to resist oxidation and scavenge free radicals. Other treatment measures included protecting mucosa and other organs and providing nutritional support.

3. Blood purification treatment: Patients were given repeated hemoperfusion from January 2019 to January 2020, and then given hemodialysis from February 2020 to January 2022 based on treatment to the control group. Femoral vein was usually chosen as the channel for blood purification, and double-lumen venous catheter, blood perfusion machine (TF-803, Zhuhai Jianfan Biotechnology Co., Ltd.) and perfusion device (HA330, Zhuhai Jianfan Biotechnology Co., Ltd.) were applied. During treatment, the blood flow rate was adjusted between 150-200 ml/min, and the treatment with each perfusion device lasted 2 hours. Meantime, hemodialysis (Germany Fresenius 4008S) and dialyze (Fresenius Yus FX60) were used. The blood flow rate was 150-200 ml/min, and the hemodialysis was conducted for 2-4 hours each time. During the treatment, heparin was usually used for anticoagulation, and the patients' blood gas and coagulation mechanism were dynamically monitored.

Collection of clinical data

The following data of patients were collected: Age, gender, body mass index (BMI), urine PQ concentration at admission, time from poison taking to gastric lavage and bowel cleanse, time from poison taking to first blood purification, total IBIrubin (TBil), direct IBIrubin (DBil), indirect IBIrubin (IBil), glutamic oxalacetic transaminase (AST), glutamic pyruvic transaminase (ALT), alkaline phosphatase (ALP), renal function-related indexes (urea nitrogen (BUN), creatinine (Cr), arterial partial pressure of oxygen (PaO_2), arterial carbon dioxide partial pressure (PaCO_2), and $\text{PaO}_2/\text{inspired oxygen (FI}O_2\text{))$, and the survival outcome of the two groups at 3 months after poison taking.

Laboratory index test

Venous blood samples (5 ml each) were collected from two groups of patients and centrifuged at 3,000 r/min for 15 minutes. After the serum was separated, the changes in patient indices, including TBil, DBil, IBil, AST, ALT, ALP, BUN, and Cr levels, were measured using the Beckman Coulter AU5800 fully automatic biochemical analyzer. The reagent kits were all provided by the instrument manufacturer.

Outcome measures

The clinical data of the two groups were compared, and the two groups were also compared in the changes of liver and kidney function before and after treatment, changes of blood gas-related indexes before and after treatment, and clinical efficacy on the two groups after treatment. Cox regression analysis was carried out to analyze the prognostic factors impacting the 3-month survival outcome of patients.

Efficacy assessment criteria

Markedly effective: clinical symptoms and signs disappeared, the breathing was basically normal, and double lung imaging examination, blood gas analysis, blood routine, liver and kidney function, myocardial enzyme spectrum, blood coagulation function were basically returned to normal; Effective: mild respiratory symptoms, alveolar-arterial PaO_2 increased, chest X-ray suggested pulmonary interstitial changes, pulmonary fibrosis but no more than 1/2 lungs, mild and moderate impairment;

Enhancing PQ poisoning survival with early repeated hemoperfusion

Table 1. Comparison of baseline data between the two groups

Factors	Control group (n=62)	The experimental group (n=87)	χ^2 value	P value
Age			1.165	0.280
> 60 years old	33	54		
≤ 60 years old	29	33		
Gender			0.814	0.366
Male	31	50		
Female	31	37		
BMI			2.556	0.109
> 25 kg/m ²	12	27		
≤ 25 kg/m ²	50	60		
Urine Paraquat concentration at admission			1.298	0.522
Low	8	12		
Middle	12	21		
High	48	54		
First time of gastric lavage and bowel cleanse			0.034	0.851
≥ 12 h	24	35		
< 12 h	38	52		
First time of blood purification			0.634	0.634
≥ 12 h	23	29		
< 12 h	39	58		

Note: BMI: body mass index.

Table 2. Comparison of treatment efficacy in patients between the two groups

Group	Markedly effective	Effective	Ineffective
Control group (n=62)	48	2	12
Experimental group (n=87)	72	12	3
χ^2 value	13.529		
P value	0.002		

Ineffective: extensive fibrosis in both lungs, multiple organ failure, acute respiratory distress syndrome; death.

Statistical analyses

SPSS 26.0 software was adopted for data process. Measurement data were described using mean \pm SD, and their comparison was conducted using the t test. Counting data were expressed as percentage and analyzed using the χ^2 test. The Kaplan-Meier survival curve was drawn for analysing the survival rate of the two groups; Cox regression analysis was conducted to determine the potential variables that affecting the mortality of patients. P < 0.05 indicated a notable difference.

Results

Comparison of clinical data

According to inter-group comparison of clinical data, the two groups were similar in baseline data, such as age, gender, BMI, urine PQ concentration at admission, first time of gastric lavage

and bowel cleanse, and first time of blood purification (all P > 0.05, **Table 1**).

Evaluation of clinical efficacy

The clinical efficacy of the two groups was evaluated after treatment. According to the results, the experimental group showed better clinical efficacy than the control group (P=0.002, **Table 2**).

Comparison of blood gas-related indexes

Before the treatment, the two groups were similar in the levels of PaO₂, PaCO₂ and PaO₂/FiO₂ (all P > 0.05, **Figure 1**), while after treatment, the levels of PaO₂ and PaO₂/FiO₂ in both groups increased notably, and the PaCO₂ level

Enhancing PQ poisoning survival with early repeated hemoperfusion

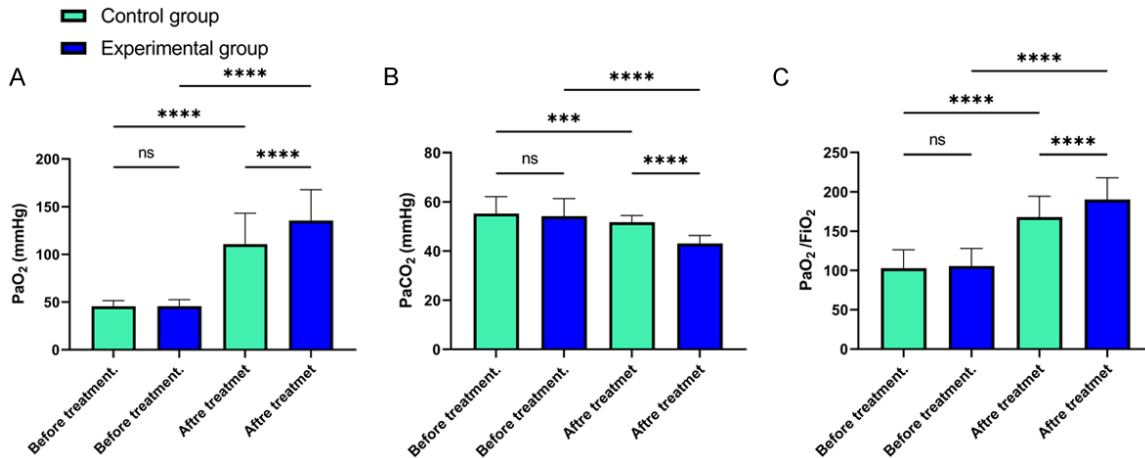


Figure 1. Changes of blood gas-related indexes before and after treatment. A: Comparison of PaO₂ between two groups before and after treatment; B: Comparison of PaCO₂ between two groups before and after treatment; C: Comparison of PaO₂/FiO₂ between two groups before and after treatment. Notes: PaO₂: Arterial partial pressure of oxygen; PaCO₂: Arterial carbon dioxide partial pressure; PaO₂/FiO₂: Arterial partial pressure of oxygen/inspired oxygen; ns > 0.05, ***P < 0.001, ****P < 0.0001.

decreased notably (all P < 0.05, **Figure 1**). According to further comparison, the experimental group showed notably higher levels of PaO₂ and PaO₂/FiO₂ and a notably lower PaCO₂ than the control group after the treatment (all P < 0.05, **Figure 1**).

Comparison of liver and kidney function

Before the treatment, the TBil, DBil, IBil, AST, ALT, ALP, BUN and Cr were not greatly different between the two groups (all P > 0.05, **Figure 2**), while after treatment, the levels of TBIL, DBIL, IBil, AST, ALT, ALP, BUN and Cr in both groups decreased notably (all P < 0.05, **Figure 2**). According to further comparison, the experimental group showed notably lower levels of TBIL, DBIL, IBil, AST, ALT, ALP, BUN and Cr than the control group after the treatment (all P < 0.05, **Figure 2**).

Analysis of factors impacting the prognosis of patients

The 3-month survival of patients was analyzed. According to the results, within 2 months, 61 patients died, showing a mortality rate of 40.93%. According to univariate Cox regression analysis, blood purification mode, age, urine PQ concentration at admission, first time of gastric lavage and bowel cleanse, first time of blood purification and DBil were the factors impacting the prognosis of patients (all P < 0.05, **Table 3**).

According to multivariate Cox regression analysis, blood purification mode, age, urine PQ concentration at admission, the first time of gastric lavage and bowel cleanse, and the first time of blood purification were independent prognostic factors (all P < 0.05, **Table 3**; **Figure 3**).

Discussion

The toxic effect of PQ on human body is mainly manifested in the damage to lung cells, which may give rise to pulmonary edema, hemorrhage, fibrous cell proliferation or hyaline membrane degeneration [12]. PQ will also damage the digestive tract mucosa, liver and kidney, which can easily bring complications such as acute respiratory distress syndrome and multiple organ dysfunction syndrome, and is life threatening [13].

The treatment of PQ poisoning entails a combination of various blood purification methods to ensure the removal of small molecular toxins and maintain the balance of water, electrolyte and acid-base [14]. Currently, the frequently adopted combined treatment schemes include hemoperfusion combined with continuous veno-venous hemofiltration, hemoperfusion combined with hemodialysis filtration and hemoperfusion combined with hemodialysis [15]. In clinical scenarios, it is usually impossible to accurately know the amount of PQ taken orally by patients, so the detected PQ in urine is

Enhancing PQ poisoning survival with early repeated hemoperfusion

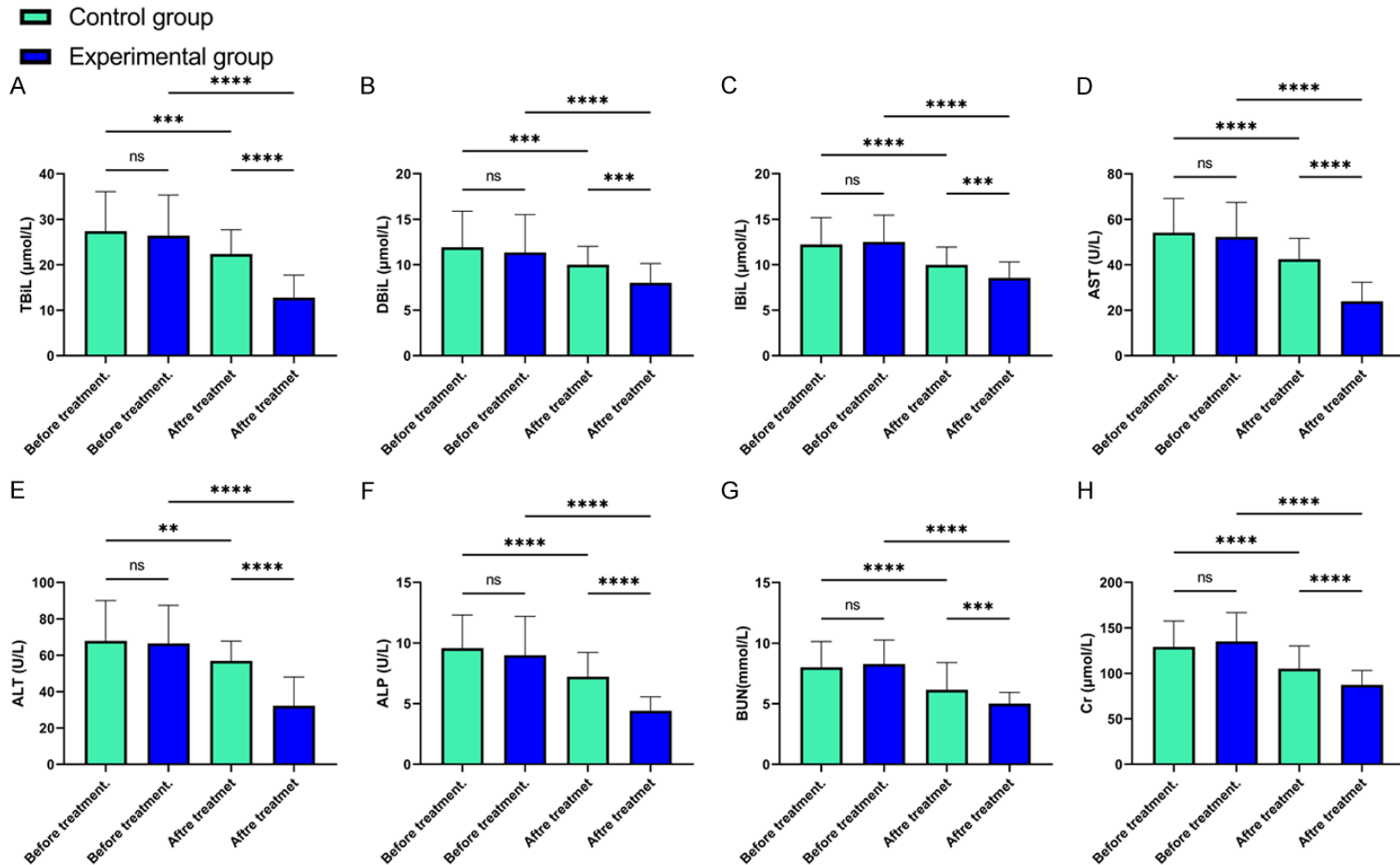


Figure 2. Changes in liver and kidney function of patients before and after treatment. A: Comparison of TBil between two groups before and after treatment; B: Comparison of DBil between two groups before and after treatment; C: Comparison of IBil between two groups before and after treatment; D: Comparison of AST between two groups before and after treatment; E: Comparison of ALT between two groups before and after treatment; F: Comparison of ALP between two groups before and after treatment; G: Comparison of BUN between two groups before and after treatment; H: Comparison of Cr between two groups before and after treatment. Notes: TBil: Total IBIrubin; DBil: Direct IBIrubin; IBil: Indirect IBIrubin; AST: Glutamic oxalacetic transaminase; ALT: Glutamic pyruvic transaminase; ALP: Alkaline phosphatase; BUN: Urea nitrogen; Cr: Creatinine. nsP > 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001.

Enhancing PQ poisoning survival with early repeated hemoperfusion

Table 3. Cox regression analysis of prognostic factors

Factors	Univariate Cox			Multivariate Cox		
	P value	HR	95% CI	P value	HR	95% CI
Blood purification mode	< 0.001	4.144	2.402-7.152	< 0.001	8.150	4.364-15.223
Age	0.042	0.593	0.359-0.980	0.035	0.578	0.347-0.963
Gender	0.098	0.653	0.395-1.082			
BMI	0.066	0.542	0.282-1.042			
Urine Paraquat concentration at admission	0.002	1.971	1.283-3.028	0.039	1.652	1.025-2.665
First time of gastric lavage and bowel cleanse	< 0.001	3.079	1.850-5.126	< 0.001	3.526	1.891-6.574
First time of blood purification	< 0.001	2.808	1.696-4.648	0.005	2.238	1.278-3.918
PaO ₂	0.400	0.984	0.948-1.022			
PaCO ₂	0.915	1.002	0.967-1.038			
PaO ₂ /FiO ₂	0.731	1.002	0.991-1.013			
TBil	0.224	0.982	0.955-1.011			
DBil	0.015	1.074	1.014-1.138	0.121	1.059	0.985-1.139
IBil	0.393	1.038	0.953-1.129			
AST	0.978	1.000	0.984-1.017			
ALT	0.565	0.997	0.985-1.008			
ALP	0.872	1.007	0.925-1.096			
BUN	0.824	1.014	0.894-1.151			
Cr	0.990	1.000	0.992-1.008			

Notes: BMI: Body mass index; PaO₂: Arterial partial pressure of oxygen; PaCO₂: arterial carbon dioxide partial pressure; PaO₂/FiO₂: Arterial partial pressure of oxygen/inspired oxygen; TBil: Total IBIrubin; DBil: Direct IBIrubin; IBil: Indirect IBIrubin; AST: Glutamic oxalacetic transaminase; ALT: Glutamic pyruvic transaminase; ALP: Alkaline phosphatase; BUN: Urea nitrogen; Cr: Creatinine.

an indicator of blood purification treatment [16]. Clinically, it is recommended to carry out treatment within 4 hours, and its therapeutic effect has been confirmed [17]. The treatment scheme needs to be adjusted according to the laboratory indicators of the patient's later. However, waiting the changes in laboratory indicators may lead to further damage to the patient's organ function and reduce the treatment effect and survival rate [18]. Therefore, early intervention is particularly crucial, and continuous elimination of toxins from the body can obviously improve the organ function of patients and improve the success rate of treatment.

In a meta-analysis, Lan et al. [19] have determined that the combination of hemoperfusion and continuous veno-venous hemofiltration markedly ameliorates the clinical outcomes in patients. In this study, we assessed the efficacy of early repeated hemoperfusion in combination with hemodialysis in patients suffering from PQ poisoning. Our results revealed that the experimental group demonstrated substantially better clinical outcomes compared to the control group. Hemodialysis employs an extracorporeal circulation device to eliminate

excess fluid and restore electrolyte balance. This process involves extracting blood from the body, purging toxic substances, and reinfusing the purified blood back into the body, thereby substituting kidney function [11]. Hemoperfusion, on the other hand, operates via adsorption to extract toxins and inflammatory mediators, thereby mitigating the ongoing detrimental impact of toxins on the patient's body [20]. The synergistic application of these two techniques effectively sustains the stability of the patients' internal environment, diminishes inflammatory symptoms, and consequently, enhances therapeutic outcomes.

Upon entering the body, PQ causes severe damage primarily on the liver, kidney, and lung tissue. This damage is discernibly reflected in laboratory biochemical indices pertaining to liver and kidney function [21]. In our study, we also evaluated the liver and kidney function and blood gas indices in both groups post-treatment. The results indicated a notable improvement in liver and kidney function indices as well as blood gas-related indices in the experimental group as compared with the control group. Dialysis can rectify acid-base imbalance and insufficient oxygenation by removing surplus

Enhancing PQ poisoning survival with early repeated hemoperfusion

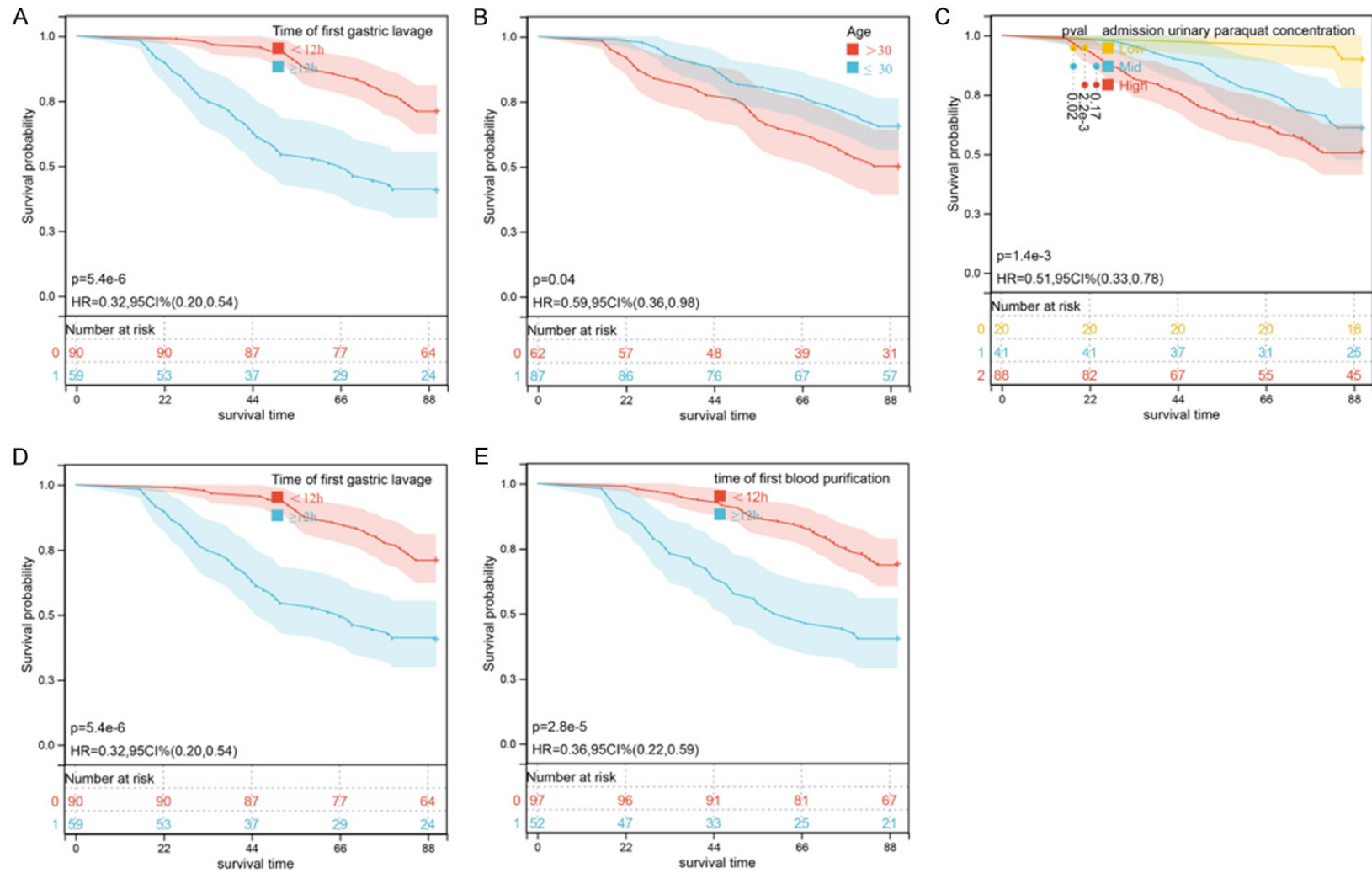


Figure 3. Prognostic factors and 90-day survival curve of patients. A: K-M curve of 90-day survival of patients with different blood purification modes; B: K-M curve of 90-day survival of patients with different ages; C: K-M curve of 90-day survival of patients with different urine paraquat concentration at admission; D: K-M curve of 90-day survival of patients with different first time of gastric lavage and bowl cleanse; E: K-M curve of 90-day survival of patients with different first time of blood purification.

Enhancing PQ poisoning survival with early repeated hemoperfusion

fluid and metabolites from the body. Similarly, early, repeated hemoperfusion combined with hemodialysis can also manage the balance of electrolytes and fluid in patients, thereby improving acid-base equilibrium and oxygenation status [22]. Moreover, this combination technique can eliminate PQ metabolites and other toxins from the body, reestablish the balance of water, electrolyte, and acid-base, effectively decreasing the burden on the liver and kidney, and aiding in the restoration of their functions [23, 24]. PQ poisoning is a severe form of acute poisoning, often leading to fatalities due to hypoxemia or multiple organ failure within days to weeks post-exposure [25]. Thus, it is vital to promptly assess the clinical outcomes and risk in critically ill patients with PQ poisoning, enabling rational allocation of medical resources.

Our study also explored the factors affecting the 90-day survival rate of patients. We identified that the mode of blood purification, patient's age, the concentration of PQ in urine at admission, the timing of first gastric lavage and bowel cleanse, and the timing of first blood purification were independent factors affecting the 90-day survival rate of patients. Corroborating previous findings by Park et al. [26] through logistic regression analysis, our study confirmed via Cox regression analysis that age is indeed an independent prognostic factor for PQ poisoning fatalities. Moreover, elderly patients, given their diminished physical function and compromised metabolic and detoxification functions of key organs such as the liver and kidneys, have a worse prognosis after PQ poisoning [27]. The concentration of PQ in the urine can provide insights into the degree of poison accumulation and organ damage in patients [28]. Previous studies have indicated that a higher urine PQ concentration at admission correlates with a worse prognosis and an increased risk of death [29]. Performing gastric lavage and bowel cleanse early can eliminate PQ in the gastrointestinal tract, reducing toxin absorption and consequent damage to the body. Delay in these procedures can allow PQ to enter the blood circulation, making its removal challenging and its impact on the body more detrimental [1]. Blood purification can effectively eliminate PQ and metabolites in the body, reducing the harmful effects of toxins and facilitating bodily recovery. A delay in blood

purification allows toxins to accumulate in the body, causing greater harm and increasing the difficulty of toxin removal, thereby heightening the risk of patient death [11].

For the first time, our study has found that early, repeated hemoperfusion combined with hemodialysis can improve the 90-day survival rate in patients, and that this combination acts as a protective factor against PQ poisoning. This could be attributed to the fact that early blood purification can effectively remove PQ and its metabolites from the body, reducing toxin-induced damage. Further, repeated blood purification helps avoiding toxin accumulation and consequent harm to the body. The combined use of hemoperfusion and hemodialysis can better maintain the stability of patients' internal environment, improve patients' inflammatory symptoms, and promote physical recovery and rehabilitation.

This study has verified the therapeutic effect of early repeated hemoperfusion combined with hemodialysis on PQ patients and their prognosis, but the study still has some limitations. First of all, in such a retrospective study, whether the collected samples based on time sequence impacts the results needs further experiments for verification. Secondly, the long-term survival of patients was not obtained in this study, so whether the treatment scheme affects the long-term survival of patients needs more data to support. Finally, whether the results of single-center research are universal still needs more data for verification. We hope to carry out more experiments in the follow-up research to improve the research conclusions.

To sum up, early repeated hemoperfusion combined with hemodialysis can substantially improve the blood gas-related indexes and liver and kidney function of patients with PQ poisoning and can also prolong their short-term survival.

Disclosure of conflict of interest

None.

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Enhancing PQ poisoning survival with early repeated hemoperfusion

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Enhancing PQ poisoning survival with early repeated hemoperfusion

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