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Early Stage Blood Purification for Paraquat Poisoning: A Multicenter Retrospective Study

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Key Words
Paraquat · Poisoning · Hemoperfusion · Continuous veno-venous hemofiltration · Conservative treatment

Abstract
Objectives: To evaluate the efficacy of conservative treatment vs. hemoperfusion (HP) vs. HP + continuous veno-venous hemofiltration (CVVH) for acute Paraquat (PQ) poisoning. ***Methods:*** This was a multicenter retrospective study of patients with PQ poisoning between January 2013 and June 2014. Clinical data and PQ serum levels were collected at baseline and after 24, 48, and 72 h of treatment. ***Results:*** Seventy-five, 65, and 43 underwent conservative treatment only (conservative treatment group), conservative treatment + HP (HP group), and conservative treatment + HP + CVVH (HP + CVVH group), respectively. PQ serum levels decreased in all groups after 72 h of treatment ($p < 0.001$); meanwhile, these values decreased faster in the HP and HP + CVVH groups compared with the conservative treatment group. More importantly, PQ blood levels were significantly lower in the HP + CVVH group compared with the HP group at 24 h ($p < 0.05$). Sequential organ failure assessment (ΔSOFA) values in the HP and HP + CVVH groups were significantly lower compared with that obtained for the conservative treatment group ($p < 0.05$). The 60-day survival rates were 21.3, 43.1 and 46.5%, respectively. Multivariate analysis indicated that age, PQ dose, admission PQ levels, and admission SOFA score were independently associated with mortality. HP and HP + CVVH were protective factors. ***Conclusion:*** Early HP or HP + CVVH after PQ poisoning could decrease PQ blood levels, alleviate organ damage, and increase survival.

Introduction

Paraquat (PQ) is a water-soluble organic heterocyclic herbicide (1,1-dimethyl-4,4-bipyridine cationic salt) with an apparent distribution volume of 1 liter/kg [1, 2]. PQ is very toxic to human and animals and is without any specific antidote. The oral lethal dose is 1–6 g and the lethal concentration is 3 g/ml [3].

The toxicity of PQ might be due to its accumulation in the alveolar cells resulting in lipid oxidation by free radicals of the cell membranes in the lung, kidney, and liver, and manifesting as pulmonary hemorrhage, edema, fibrosis, and liver and kidney damage [4]. Treatments include emetics, gastric lavage, catharsis, diuretics, reduced glutathione, glucocorticoid, and organ function support [5–7].

The toxicokinetics of PQ in humans is not entirely clear, and most knowledge is obtained from animal studies. The gastrointestinal absorption rate of PQ is low and most of PQ is excreted through the feces. The peak serum concentration appears 2–4 h after oral absorp-

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tion. PQ binds weakly to plasma proteins and is not reabsorbed in the renal tubules. The kidney is the organ with the highest concentration of PQ and the main organ responsible for PQ excretion. The clearance rate of PQ is associated with the kidney function. The lethal concentration in the lung tissues can be reached within 6 h in case of severe PQ poisoning. PQ levels in muscles are also relatively high. Lung and muscle become a reservoir of PQ, releasing it into the blood as the kidneys clear it [8].

Blood purification of PQ poisoning is controversial [8]. Hemoperfusion (HP) can be used to treat PQ poisoning at the early stage [8–10], but HP is more suitable for poisons with a large molecular mass, that are lipid soluble, and with a high protein binding rate [11], which is not the case for PQ. On the other hand, continuous veno-venous hemofiltration (CVVH) is more efficient for clearing water soluble, small molecular poisons with a low protein binding rate [11], but there is lack of data for the use of CVVH in PQ poisoning.

Therefore, the aim of this retrospective study was to examine the efficacy of conservative treatment, HP, and HP + CVVH for the early treatment of PQ poisoning.

Materials and Methods

Patients

This was a retrospective study of consecutive patients with acute PQ poisoning treated at the Beijing Chaoyang Hospital, The Second Affiliated Hospital of Hebei Medical University, Cangzhou People's Hospital of Hebei Province, and Shangdong Province-Owned Hospital between January 2013 and June 2014.

Inclusion criteria were as follows: (1) PQ poisoning by oral intake; (2) aged >14; (3) admission within 24 h of PQ poisoning; and (4) urine concentration of PQ was 5–200 μg/ml by the semi-quantitative sodium bisulfite method. Exclusion criteria were as follows: (1) combined with the other poisonings; (2) hypersensitivity to heparin; (3) history of heparin-induced thrombocytopenia; (4) significant bleeding tendency; (5) history of severe diseases of the heart, lung, liver, kidney, or hematological system; (6) pregnant or lactating; (7) multiple organ failure; or (8) refusal of active therapy, for example, due to economic reasons.

This study was approved by the Ethics Committees of each participating hospital. The need for individual consent was waived off by the committees because of the retrospective nature of the study.

Grouping

The patients were classified according to the treatment they received: conservative treatment (conservative treatment group), conservative treatment + HP (HP group), or conservative treatment + HP + CVVH (HP + CVVH group). The selection of the treatment was made by the attending physician after discussion with the patients and their families after considering the condition of the patients and their financial status.

Treatments

For conservative treatment, patients received an emetic (sodium bicarbonate solution or activated carbon suspension of 200 ml injected into the stomach); gastric lavage (15% bleaching clay suspension or 15% activated carbon suspension); catharsis (15% bleaching clay suspension or 15% activated carbon suspension, 300 ml with 20% mannitol, 250 ml); promotion of PQ excretion by fluid infusion and diuresis. Organ function supportive therapy included oxygen supply, mechanical ventilation, expanding blood volume, and administration of vasoactive drugs to maintain appropriate tissue perfusion and cell metabolism when necessary.

For the HP group, conservative treatment was administered as mentioned above; central venous access was achieved by indwelling a double lumen catheter within 1 or 2 h after admission. The HP treatment was carried out with the HA330 neutral resin perfusion apparatus (Jafron Biomedical Co., Ltd., Zhuhai, China). Blood flow was set at 150–200 ml/min, and each session lasted 3–4 h. The first treatment was conducted on the day of admission, the second treatment 6–8 h later, and subsequent treatments once on days 2 and 3. Heparin was intravenously injected before HP using a loading dose of 0.5 mg/kg and continuous intravenous injection using a maintenance dose of 10–20 mg/h. Heparin was stopped 30 min before HP completion.

For the HP + CVVH group, conservative treatment was administered as mentioned above; HP lasting 3–4 h was performed on the day of admission, with CVVH immediately conducted for 72 h. Before HP and CVVH, vascular access was obtained using an 11.5F double-lumen catheter (Teleflex, Arrow, USA). The extracorporeal circulation line and filter (AV600S, Fresenius, Germany) were washed with 100 mg heparin dissolved in 2,000 ml normal saline before CVVH. Postdilution CVVH was performed at a blood flow rate of 150–200 ml/min; ultrafiltration rate was 25–30 ml/kg/h for each new circuit. Circuits were disconnected at high prefilter (>280 mm Hg) or transmembrane (>280 mm Hg) pressure. After disconnection, a new circuit was immediately initiated until CVVH was completed. A 1.4 m^2 polysulfone membrane filter (AV600S, Fresenius, Germany) and CRRT device (Multifiltrate, Fresenius, Germany) were used. Replacement fluids were heated to 39°C; a combination buffer containing 113 mmol/l Na^+, 3.0 mmol/l K^+, 0.797 mmol/l Mg^{2+}, 118 mmol/l Cl^-, 1.5 mmol/l Ca^{2+}, 10.6 mmol/l anhydrous dextrose, and bicarbonate-buffered fluids were used post-filtration, adjusted by plasma bicarbonate levels and pH according to blood gas data. Heparin was intravenously injected at a loading dose of 25–30 IU/kg, and continuous intravenous injection occurred at a maintenance dose of 5–10 IU/kg/h until CVVH was completed.

Data Collection

Baseline patient data were collected including age, gender, dose of PQ, blood levels of PQ at admission, serum levels of superoxide dismutase (SOD), white blood cell counts, platelets counts, blood glucose level, serum levels of creatinine (Cr), alanine aminotransferase, and amylase. The score of acute physiology and chronic health status (APACHE-II) was assessed as well. The serum levels of PQ were monitored and the score of sequential organ failure assessment (SOFA) was calculated at 24, 48, and 72 h after admission [8, 12]. ΔSOFA was defined as the differences between the SOFA scores at 24 and 72 h. The patients were followed up for 60 days. Mortality was recorded.

Table 1. Baseline characteristics of the patients with acute PQ poisoning according to subsequent treatments

Parameters	Conservative treatment (n = 75)	HP treatment (n = 65)	HP + CVVH treatment (n = 43)	p value
Gender, n (%)				
Man	35 (46.7)	36 (55.4)	25 (58.1)	0.409
Woman	40 (53.3)	29 (44.6)	18 (44.6)	
Age, years	36 (18–56)	36 (16–52)	38 (18–60)	0.782
Time to admission, h	12.2 (0.5–22.0)	7.5 (0.5–20.5)	7.8 (0.5–19.0)	0.106
Dose, ml	96 (5,250)	87 (2,200)	66 (5,200)	0.176
PQ blood levels at admission, μg/ml	21.6 (0.3–100.2)	23.0 (0.6–124.5)	20.8 (0.9–200.6)	0.071
WBC, $\times 10^9$/l	14.2±6.8	16.1±9.9	15.3±5.9	0.073
SOD, U/g	177.1±51.7	200.0±77.9	177.3±23.6	0.106
APACHE-II score	3 (0–8)	3 (0–11)	3 (0–9)	0.208
SOFA score at 24 h after admission				
Respiratory score	1.5 (0–3)	1.7 (0–4)	0.9 (0–3)	0.732
Coagulation score	0.1 (0–1)	0.5 (0–2)	0.6 (0–3)	0.021
Liver function score	0.4 (0–3)	0.5 (0–3)	0.7 (0–3)	0.414
Blood circulation score	0.9 (0–3)	1.0 (0–3)	0.9 (0–3)	0.732
CNS function score	0.1 (0–2)	0.1 (0–2)	0.1 (0–2)	0.526
Kidney function score	0.4 (0–3)	0.5 (0–3)	0.2 (0–3)	0.927
Total score	3.0 (0–9)	2.9 (0–7)	3.1 (0–10)	0.212

WBC = White blood cells. Data are presented as median (minimum–maximum) or as mean ± SD.

Serum Levels of PQ

Total blood samples were obtained with heparin anti-coagulation, stored at –80°C, and sent on ice for detection within 72 h. Quantitative and qualitative analysis of PQ in blood was performed according to previously published methods [13].

Statistical Analysis

Continuous data were tested for normality using the Kolmogorov–Smirnov test. Normally distributed continuous data are presented as mean ± SD and were analyzed using analysis of variance (ANOVA) with the Student–Newman–Keuls post hoc test or repeated measures ANOVA with Bonferroni post hoc test, as appropriate.

Non-normally distributed continuous data are presented as median (range) and were analyzed using the Kruskal–Wallis test. Categorical data are presented as frequencies and were analyzed using the chi-square test. The risk factors for death and prognosis were assessed by univariate and multivariate non-conditional logistic regression. The survival curves were made by the Kaplan–Meier method and compared using the log-rank test. Statistical analysis was performed using SPSS 18.0 (IBM, Armonk, N.Y., USA). Two-sided p values <0.05 were considered statistically significant.

Results

Characteristics of the Patients

Seventy-five (41.0%), 65 (35.5%), and 43 (23.5%) patients were in the conservative treatment, HP, and HP + CVVH groups, respectively. There were no differences among the 3 groups in terms of gender distribution, age, time to admission (time elapsed from PQ poisoning to hospital admission), dose of PQ, blood levels of PQ at admission, serum levels of SOD, APACHE-II score, white blood cell counts, and SOFA score at admission (all $p > 0.05$; table 1).

Blood Levels of PQ

There were no significant differences among the 3 groups at admission ($p > 0.05$; table 2). Blood levels of PQ were significantly lower in the HP and HP + CVVH groups at 24, 48, and 72 h after admission in comparison with the conservative treatment group ($p < 0.05$); in addition, PQ blood levels were significantly lower in the HP + CVVH group compared with the HP group at 24 h ($p < 0.05$). The blood levels of PQ were decreased in all 3 groups after 3 days of treatment, though the blood levels of PQ were lower in the HP and HP + CVVH groups 72 h after admission compared with the conservative treatment group ($p < 0.05$).

SOFA Scores

SOFA scores at admission and at 24, 48, and 72 h after admission are presented in table 3. There were no significant differences among the 3 groups regarding SOFA scores at 24 h ($p > 0.05$). ΔSOFA values in the HP and

Table 2. Blood levels of PQ comparison at baseline and during treatment

Group	n	Baseline	24 h	48 h	72 h	p value
Conservative	75	21.56±11.17	16.71±8.35[a]	10.33±6.67[a, b]	6.02±3.29[a–c]	<0.001
HP	65	22.95±10.41	7.84±3.63*, [a]	4.54±2.58*, [a, b]	2.50±1.34[a–c]	<0.001
HP + CVVH	43	20.82±9.26	4.95±2.81*, #, [a]	3.91±1.89*, [a, b]	2.11±1.67[a–c]	<0.001
p value	–	0.553	<0.001	<0.001	<0.001	

All data are presented as mean ± SD, μg/ml.
* $p < 0.05$ vs. conservative treatment; # $p < 0.05$ vs. HP; [a] $p < 0.05$ vs. before baseline; [b] $p < 0.05$ vs. 24 h; [c] $p < 0.05$ vs. 48 h.

Table 3. SOFA score during treatment

	Conservative treatment (n = 75)	HP treatment (n = 65)	HP + CVVH (n = 43)	p value
24 h	3.03±2.06	2.97±1.82	3.06±2.04	0.763
48 h	4.07±2.72	4.54±3.22	4.81±3.70	0.759
72 h	5.76±3.29	4.43±3.1*	4.93±3.57*	<0.001
ΔSOFA	3.34±1.69	1.72±1.05*	2.11±1.28*	<0.001

All data are presented as mean ± SD, score.
* $p < 0.05$ vs. conservative treatment.

HP + CVVH groups were significantly lower than in the conservative treatment group ($p < 0.05$), but there were no significant differences between the HP and HP + CVVH groups ($p > 0.05$).

Survival

The 3-day survival rates were 86.0 and 65.1% for the HP and HP + CVVH groups, and were significantly higher than those of the conservative treatment group (56.0%) ($p < 0.05$). The 7-day survival rates were 56.9 and 65.1% for the HP and HP + CVVH groups, and were significantly higher than those of the conservative treatment group (41.3%) ($p < 0.05$). The 60-day survival rates were 43.1 and 46.5% for the HP and HP + CVVH groups, and were significantly higher than those of the conservative treatment group (21.3%, $p < 0.05$). However, there were no significant differences between the HP and HP + CVVH groups at any time point ($p > 0.05$).

The 60-day survival curve is shown in figure 1. Median survival times were 3, 15, and 40 days for the conservative treatment, HP, and HP + CVVH groups, suggesting that blood purification could significantly improve survival. Median survival was significantly longer in the HP ($p = 0.003$) and HP + CVVH ($p = 0.001$) groups compared with the conservative treatment group, but without difference between the HP and HP + CVVH groups ($p = 0.535$).

Analysis of Risk Factors for Death

Tables 4 and 5 present univariate and multivariate analyses of factors associated with 60-day mortality, respectively. Factors significantly associated with mortality in univariate analyses (table 4) were included in the multivariate model. Results showed that age (OR 1.128, 95% CI 1.030–1.235), PQ dose (OR 1.076, 95% CI 1.020–1.136), PQ serum levels at admission (OR 1.539, 95% CI 1.142–2.073), and SOFA score at admission (OR 8.073, 95% CI 1.515–43.006) were independently associated with mortality, while HP (OR 0.316, 95% CI 0.119–0.838) and HP + CVVH (OR 0.297, 95% CI 0.111–0.795) were protective factors (table 5).

Discussion

This study showed that conservative, HP, and HP + CVVH treatments all decreased PQ serum levels and improved SOFA scores. HP and HP + CVVH treatment

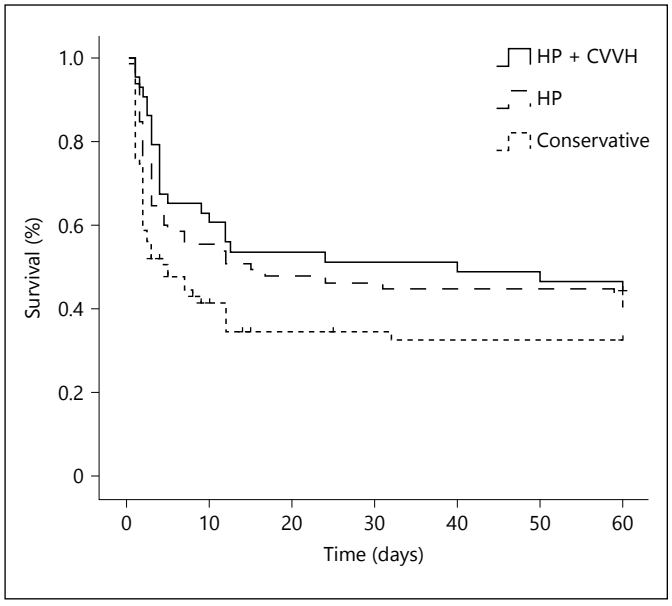

Fig. 1. Sixty-day survival according to treatment after acute PQ poisoning.

were better than the conservative therapy; HP and HP + CVVH groups were similar in most parameters studies. However, PQ blood levels were significantly lower in the HP + CVVH group compared with the HP group at 24 h. Multivariate analysis indicated that age, PQ dose, PQ serum levels at admission, and SOFA score at admission were independently associated with mortality, while HP and HP + CVVH were protective factors. These results suggest that early HP or HP + CVVH after PQ poisoning could decrease PQ blood levels, alleviate organ damage, and improve survival.

PQ undergoes almost no biological transformation in vivo and 90% is excreted through the kidneys. PQ uptake by alveolar epithelial cells is an energy-dependent active process, and the peak concentration in lungs can be reached within 15 h, up to concentrations as high as 10–90 times the serum levels [8, 12]. Therefore, lung and muscle tissues are regarded as reservoirs for PQ, which is released into the blood once the plateau is reached. Acute respiratory distress syndrome was reported to occur in patients with acute PQ poisoning, and the mortality rate can be as high as 50–80% [6]. Hemodialysis (HD), HP, and CVVH are commonly used blood purification methods for PQ poisoning. It is widely accepted that HP is more effective than HD for PQ poisoning; indeed, the clearance rate of HP is about 5–7 times that of HD [1], and HP is still effective when blood levels of PQ are lowered to <0.2 mg/l [14].

Table 4. Univariate analysis of factors involved in mortality after acute PQ poisoning

Parameters	OR	95% CI		p value
		lower	upper	
Gender	1.347	0.741	2.446	0.328
Age	1.055	1.032	1.079	<0.001
Time to admission	0.955	0.921	0.990	0.012
Dose	1.031	1.020	1.043	<0.001
Times of blood perfusion	0.879	0.691	1.119	0.295
CVVH times	0.823	0.441	1.536	0.541
PQ blood levels at admission	1.240	1.135	1.354	<0.001
SOD	0.994	0.986	1.001	0.099
Blood purification (control)				0.006
HP	0.358	0.171	0.750	0.006
HP + CVVH	0.312	0.138	0.705	0.005
SOFA score at 1st day	2.015	1.545	2.629	<0.001
WBC	0.908	0.864	0.953	<0.001
Platelets	0.999	0.995	1.003	0.509
Neutrophils	1.008	0.982	1.035	0.536
Blood glucose	0.817	0.737	0.905	<0.001
Blood Cr	0.999	0.995	1.003	0.776
ALT	0.994	0.985	1.003	0.176
Hemodlastase	1.000	0.998	1.002	0.889

WBC = White blood cells; ALT = alanine aminotransferase.

Table 5. Multivariate analysis of factors involved in mortality after acute PQ poisoning

Parameters	OR	95% CI		p value
		lower	upper	
Age	1.128	1.030	1.235	0.009
Time to admission	0.923	0.772	1.104	0.380
Dose	1.076	1.020	1.136	0.007
PQ blood levels at admission	1.539	1.142	2.073	0.005
Blood purification (control)				0.025
HP	0.316	0.119	0.838	0.021
HP + CVVH	0.297	0.111	0.795	0.016
SOFA score at 1st day	8.073	1.515	43.006	0.014
WBC	1.076	0.889	1.304	0.451
Blood glucose	1.023	0.783	1.337	0.868

WBC = White blood cells.

However, PQ is a small water soluble molecule with a low protein binding rate, and secondary distribution can be observed. Theoretically, clearance effectiveness of CVVH is superior to that of HP. Therefore, in this study, results indicated that the blood levels of PQ were significantly decreased within the first 3 days after admission,

and that the blood levels of PQ were significantly lower in the blood purification groups (HP and HP + CVVH) compared to the conservative treatment group at 24, 48, and 72 h after admission, suggesting that blood purification could rapidly reduce the blood levels of PQ, which is supported by Pond et al. [12]. Multivariate analysis showed that HP and HP + CVVH treatments were associated with lower mortality.

Nevertheless, no matter the blood purification method (HP, CVVH, or HD), the sooner the blood is purified, the better the outcome. It was reported that though HD and HP could decrease the severity of PQ poisoning and prolong survival, mortality was not decreased [8, 15]. This might be ascribed to the fact that lethal amounts of PQ had started entering into the alveolar epithelial cells and major organs, with blood purification not able to alter the toxicokinetics of PQ in these conditions [8, 12]. The secondary distribution of PQ from lung and muscle tissues to blood circulation could be observed once the blood levels started to decrease; therefore, the timing and duration of blood purification may be very important [16, 17]. Generally, blood purification is recommended to be performed as soon as 4–12 h after PQ poisoning, and the earlier the better [16, 17]. Since it takes time for PQ to diffuse from tissues to blood, it might be necessary to continue blood purification [1].

HP was conducted only once on the day of admission in the HP + CVVH group, and then CVVH was immediately performed for 72 h, while HP was carried out once a day within the first 3 days of admission in the HP group. Finally, this study indicated that the PQ clearance rate was equivalent between HP and HP + CVVH, except for the first 24 h, where a faster rate was obtained in the HP + CVVH group; in addition, no significant differences in 60-day survival were observed. Compared to HP, HP + CVVH has some merits [17]: (1) PQ is removed continuously to maintain hemodynamics; (2) CVVH corrects the imbalances in water, electrolytes, and acid-base equilibrium; and (3) CVVH continuously removes metabolites such as urea and Cr. Since HP cannot correct water, electrolyte, and acid-base equilibrium imbalances, HP + CVVH should be prioritized for treating PQ poisoning. However, randomized control studies are needed to evaluate the effects of CVVH alone on PQ poisoning.

Limitations

This study does have some limitations. First, the sample size was relatively small. Second, this was a retrospective study with all the inherent biases and limitations. Third, given the limitation of financial resources of some patients, a bias could have been introduced leading to more wealthy and healthy patients to undergo HP + CVVH. Fourth, urine concentrations of PQ in the study population were 5–200 μg/ml; therefore, the study results could not be extrapolated for urine concentrations of PQ >200 μg/ml observed in severe PQ poisoning. Fifth, time to admission was higher in the conservative treatment group compared with values obtained for the HP and HP + CVVH groups, although the differences were not statistically significant; whether this has contributed to our results merits further assessment. Finally, the toxicokinetics of PQ is still poorly understood, limiting the application of treatments. Additional studies are still necessary to determine the best course of action for acute PQ poisoning.

Conclusion

HP or HP + CVVH could rapidly decrease the blood levels of PQ at the early stage, alleviate organ injuries, and improve survival. The therapeutic effect was mostly equivalent between HP and HP + CVVH treatment regarding to the acute PQ poisoning, especially after the first day of treatment. Age, dose, blood levels of PQ at admission, and SOFA score at 24 h after admission were independent risk factors for mortality, while HP and HP + CVVH were independent protective factors.

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Disclosure Statement

The authors declare that they have no conflict of interests.

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