

**The Efficacy of Initial Hemopurification Strategy for Acute
Paraquat Poisoning in Adults: Study Protocol for a Randomized
Controlled Trial (HeSAPP)**

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NCT03314909

PROTOCOL

Study setting

Patient recruitment would be completed in The First Affiliated Hospital of Zhengzhou University, a comprehensive tertiary medical center in Henan Province, China with 50 beds in emergency intensive care units (EICU). The estimated number of admitted acute paraquat poisoned patients ranges from 50-200 persons per year. To assist participant enrolment, after acceptance of this protocol, a notice of this trial would be sent to the Emergency Room (ER) of all secondary hospitals in Henan Province to improve transference to the First Affiliated Hospital of Zhengzhou University. Considering the fact that intervention would be administered in ER setting, and the relatively short duration of assigned hemopurification, adherence of patients is promising. Patients' families would receive full explanation of treatment plan and continuous follow-up in order to promote adherence.

Study population

Upon admission to ER, patients suspected with PQ intoxication would receive a urine dithionite test, and only those with a positive result would be invited to participate in this trial. The urine dithionite test would be measured by Spectrophotometer Type 721, and the minimal measurable concentration of paraquat is 0.2 µg/ml. Detailed inclusion and exclusion criteria are listed as follows.

Inclusion criteria

Patients meeting with all of the following criteria would be included in this trial: (1) Suspected paraquat ingestion history (intended or accidental), which is confirmed by positive urine dithionite result (light blue, navy blue and dark blue). (2) Arriving at the ER within 24 hours after PQ digestion. (3) Age: 18 ~-70 years old. (4) No known current pregnancy or lactation. (4) Absence of cardiac arrest after poisoning, and no previous or present history of chronic kidney disease, chronic liver disease, respiratory failure, COPD, asthma, heart failure, pancreatic disease, acute coronary syndrome (ACS) or stroke. (5) No known combined ingestion with other poisons or alcohol. (6) No previous blood purification treatment prior to admission. (8) No known participation in other medical trials. (9) Agreement on informed consent.

Exclusion criteria

Patients in any one of the following conditions would be excluded: (1) Patients who are unable to comply with the procedures of the present trial, including those who change therapy or withdraw treatment. (2) Patients who develop severe allergic response to HP materials. (3) Patients who do not receive intervention within 4 hours after admission in reality.

Allocation randomization and concealment

All participants would be randomly stratified into three blocks according to the result of urine dithionite test, i.e. light blue, navy blue and dark blue. Block length is set at 12. With the help of SAS 9.3, patients in different blocks would be allocated to four groups, namely the hemodialysis group (HD group), hemoperfusion group (HP group), concurrent hemodialysis and hemoperfusion group (HP-HD group), and conservative therapy group (control group), at a 1:1:1:1 ratio(Figure 1).

Due to the apparently different equipment of the interventions, it would be impractical to blind the present trial, therefore both patients and physicians would be aware of the exact treatment that the patients would receive. A sealed envelope with the allocation information would then be sent to the physician in charge of the patient after stratified grouping. To reduce assessor bias, blood samples and chest radiograph would be collected and examined by staff independent of this study.

Intervention

The intervention under investigation includes conservative therapy, hemoperfusion alone, hemodialysis alone, and hemoperfusion and hemodialysis concurrent therapy under the Guideline of Chinese Blood Purification for Acute Paraquat Poisoning Patients.

Study procedure

Physicians involved in the study would receive standardized training in carrying out this trial. Upon enrollment, informed consent, basic demographic information and collateral history would be taken from the patients or their next of kin (Table 1). PQ ingestion volume would be estimated as follows: 1 mouthful of liquid for women= 22 ml and 1 mouthful for men =28 ml . PQ ingestion amount, defined as PQ concentration \times PQ ingestion volume, would be calculated. Physicians would also assess the participants by various scores (Table 2), including Acute Physiologic and Chronic Health Evaluation (APACHE II) score and Poisoning Severity Score (PSS).

Upon suspected diagnosis of PQ poisoning, all patients would receive gastric lavage with room warm water (≥ 5 L), and 1g/kg active charcoal via nasogastric tube. After confirmed diagnosis by urine dithionite test, intervention would be initiated upon acquisition of informed consent and randomized allocation, which would take less 1 h after admission ideally. Subsequent treatment varies by groups:

- (1) **HD group:** participants would receive 4 hours of HD therapy a day for three consecutive days.
- (2) **HP group:** participants would receive 4 hours of HP a day for three consecutive days.

- (3) **HP-HD group:** participants in this group would receive 4 hours' hemoperfusion and hemodialysis concurrent therapy for consecutively three days.
- (4) **Control group:** participants in this group would receive conservative treatment (see below).

According to the Chinese Guideline on Management of Paraquat Poisoning, all patients groups would receive standard treatment as follow. Methylprednisolone 15mg/kg/d together with cyclophosphamide 15mg/kg/d would be administered for the first week. After the first week, methylprednisolone would be reduced by 40 mg every 3 days, while no more cyclophosphamide would be given. Patients would be given supplemental oxygen only if their PaO_2 falls below 40mmHg or in the cases of Acute Respiratory Dyspnea Syndrome (ARDS).

Procedure of HD

- (1) Preparation: Place a dual-lumen catheter in the internal jugular vein, or place a dual-lumen catheter in the femoral vein if needed. Equip the hemodialysis machine (HD machine: Fresenius 4008s. Cartridge: Fresenius Fx60. Both by Fresenius Medical Care AG Co, Germany). Rinse the pipeline with 1L of normal saline (NS) at a speed of 100 ml/min. Set the volume of dialysis at 300 ml, and run the dialysis machine in close loop for 10 min.
- (2) Anticoagulation: Inject 60-80 IU/kg low molecular weight heparin (LMWH) 20-30 min before hemodialysis.
- (3) Therapy and surveillance: connect the pipeline to the catheter, and run the dialysis machine at a speed (ml/min) 4 times as the patient's weight (kg). Dialysis solution speed should be set at 500 ml/min. Run hemodialysis for 4 hours meanwhile closely monitor the patients' vital signs. During HD, anticoagulation function should be monitored by transmembrane pressure (TMP) of dialyzer. If $\text{TMP} > 250\text{mmHg}$, additional LMWH should be added.

Procedure of HP

- (1) Preparation: Establish a dual-lumen catheter in the internal jugular vein, or in the femoral vein if needed. Equip the hemoperfusion machine (HP machines: Jaftron model JF-800. Cartridge: HA330. Both by Jaftron biomedical.co.). Rinse the whole pipeline with 5% glucose solution at a speed of 100 ml/min until the pipeline is filled with glucose solution. Then rinse pipeline with NS at a speed of 200 ml/min. The total volume used for rinsing is 2000 ml.
- (2) Anticoagulation: Rinse the pipeline with 500ml NS mixed with 4 mg/dl heparin. Ten minutes later, rinse the pipeline with 300 ml NS. Connect the pipeline to the catheter on the patient. Inject 0.5-1.0 mg/kg heparin, then add heparin at a speed of 10-20 mg/h based on coagulation status (keep activated partial thromboplastin time (APTT) 50% above upper limit of normal). Stop adding heparin 30 min before the end of each course.
- (3) Surveillance: Run HP for 4 hours a day. Monitor vital signs during HP and prevent hypotension. Optimal flow velocity of extracorporeal blood flow ranges from 100 to 200 ml/min. Change the hemoperfusion cartridge as soon as any charcoal appears in the blood flow.

Procedure of HP-HD

- (1) Preparation: Place a dual-lumen catheter in the internal jugular vein, or in the femoral vein if needed in ER. Equip the blood purification machines (HP and HD machines and cartridges as mentioned above). The outlet of the HP cartridge should be connected with the inlet of HD machine. Rinse HP pipeline and HD pipeline with 1L of NS mixed with 3000 IU heparin at a speed of 100-150 ml/min, followed by 600ml of NS containing 3000 IU heparin.
- (2) Anticoagulation: Inject LMWH 50-60 IU/kg as loading dose, then maintain at a speed of 400 IU/h and adjust dose according to transmembrane pressure (keep TMP \leq 250mmHg).
- (3) Run HP-HD: Connect the inlet of the HP cartridge to the catheter, and run the machine for 4 hours. Blood flow speed ranges from 100 to 200 ml/min. Dialysis solution speed is 500 ml/min. Hemoperfusion cartridge should be changed as soon as any charcoal appears. Patients' vital signs should be monitored during treatment.

Monitoring

Arterial blood gas test, complete blood count, coagulation function test, liver function, pancreatic function would be performed and urine volume would be taken every day before hemopurification (if there is any). Urine dithionite test result would be recorded every 4-6 hours from admission until there are three consecutive negative results. Renal function would be tested daily. Chest radiographs would be taken once a week or as soon as the patient deteriorates. If any patient develops fever or sepsis during treatment, they would be investigated to identify potential catheter-related bloodstream infection. Ultrasound for lower limb deep veins would be administered for patients with notable increase of calf/thigh circumference to identify thrombogenesis.