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Efficacy of initial haemopurification strategy for acute paraquat poisoning in adults: study protocol for a randomised controlled trial (HeSAPP)

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ABSTRACT

Introduction Paraquat (PQ) is a widely used herbicide which is inexpensive and easily accessible for people in rural areas. A small amount of PQ ingestion could be lethal, yet currently, the optimal treatment is still controversial. Extracorporeal therapies (ECTR) have been practised in PQ poisoning management, though limited evidence could be obtained to suggest its superiority over conservative therapy. Haemodialysis (HD) and haemoperfusion (HP) are most commonly used, while some institutions also choose HP–HD concurrent therapy. The object of the present trial is to investigate whether haemopurification therapy can reduce mortality compared with conservative therapy.

Methods and analysis This is a planned single-centre, non-blinded, randomised controlled trial. Acute PQ poisoned adults who have orally ingested PQ within 24 hours would be recruited. A total of 360 patients would be recruited and randomly assigned to four groups, that is, HP, HD, concurrent HP–HD and control, at a 1:1:1:1 ratio. Subjects would be also stratified by their urine dithionite test results. Primary outcome is 28-day all-cause mortality. Secondary outcomes include survival time, all-cause mortality at the 3rd, 7th and 60th day, rate of major complications, Acute Physiologic and Chronic Health Evaluation score and Poisoning Severity Score, etc.

Ethics and dissemination The protocol and informed consent documents have been approved by the Ethics Committee of The First Affiliated Hospital of Zhengzhou University in September 2017 (approval number: 2017-KY-10). The result of this trial would be submitted to peer-reviewed journal.

Trial registration number NCT03314909; Pre-results.

Strengths and limitations of this study

- This is the first parallel randomised controlled trial to compare the efficacy of haemoperfusion (HP), haemodialysis (HD), concurrent HP–HD and non-haemopurification treatment in acute paraquat (PQ) poisoning.
- Patients will be stratified by the result of urine dithionite test.
- The primary outcome is 28-day mortality.
- Subgroup analysis based on time lapse from PQ ingestion to treatment may provide reference for initiation time of haemopurification.
- The limitation of this study is the unavailability of serum PQ concentration.

INTRODUCTION

Among 1.6 million violent deaths every year in the world, half are suicidal and 63% of these occur in the Asia-Pacific region.[1] Pesticide suicide accounts for up to one-third of all suicides worldwide every year.[2] Being inexpensive and easily accessible, paraquat (PQ), a water-soluble toxic organic herbicide (1,1-dimethyl-4,4-bipyridine cationic salt) is still widely consumed in some countries like China, and occasionally serves as poison.[3]

A very small amount of PQ can cause death in human. A study of 375 participants reports that patients with a plasma PQ concentration higher than 3.44 µg/mL died,[4] though some other studies indicate a relative higher upper limit for survivors.[5 6] The mortality of PQ is remarkably high (ranging from 42.7% to 90%[7–9]), but unfortunately, there is still no effective treatment for confirmed PQ poisoning. The main mechanism of PQ intoxication is generation of free radicals and oxidative stress, and some studies claim that immunosuppressive therapy can improve survival rate.[9 10] Considering the physical characteristics of PQ, for example, relatively low volume of distribution (1.2–1.6 L/kg),[3] low molecular weight and low protein binding rate, it is reasonable to propose that extracorporeal theraphies (ECTR) may benefit patients with PQ poisoning.

Haemodialysis (HD) purifies blood by filtering poisonous molecules through a

selectively permeable membrane, especially molecules with a small molecular weight and low protein binding rate. It can also correct acid–base disturbance in patients. Theoretically, HD should be the ideal treatment for acute PQ poisoning in view of its physical characteristics. However, HD is not widely applied in practice, and the Expert Consensus on Acute PQ Poisoning in China recommends HD as a supplementary therapy for patients complicated with acid–base disturbance.[11] Little evidence could be obtained in HD for PQ poisoning treatment in the last 30 years. In an experimental model, it is demonstrated that after 90 min of HD, PQ clearance remains static in vitro (179 mL/min).[12] Compared with the high apparent renal clearance of PQ (1.17 L/hour) in vivo,[13] HD seems to have a limited effect on PQ clearance, probably due to the limitation of HD filter material. With the improvement in filter, HD has a twofold increase in small molecule clearance compared with 40 years ago[14]; thus, further research is needed to evaluate the treatment effect of HD in PQ poisoning management.

Haemoperfusion (HP) removes blood toxicants by absorbing them through a column and is another choice for PQ poisoning treatment. As it has a superior PQ clearance over HD in vivo,[12] it has become the standard treatment for PQ intoxication in many countries.[11 15] Several retrospective studies report that HP could significantly improve PQ plasma clearance and reduce mortality compared with control groups,[16 17] while other studies point out that patients would benefit from HP only when it is administered early from the onset of poisoning.[12 18 19] In one prospective clinical trial, Li *et al* reports that HP could enhance PQ clearance, but no conclusion was drawn on mortality.[20] In addition, the toxicokinetics of PQ during HP are poorly understood. Although some evidence from China suggests that HP and HD concurrent therapy (HP–HD) can significantly reduce mortality,[21–25] it is not a standard therapy in PQ poisoning. High costs and long therapeutic duration may have hindered its application in clinical practice.

The hypothesis of the present study is that early haemopurification therapies may reduce mortality in acute PQ poisoned patients. This is a single-centre, parallel, non-blinded randomised controlled trial to investigate the superiority of HD, HP and HP–HD concurrent therapy compared with conservative therapy during acute PQ poisoning. Allocation ratio of each group is 1:1:1:1.

METHODS AND ANALYSIS

Study setting

Patient recruitment would be completed in The First Affiliated Hospital of Zhengzhou University, a comprehensive tertiary medical centre in Henan Province, China, with 50 beds in emergency intensive care units (EICU). The estimated number of admitted acute PQ poisoned patients ranges from 50 to 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 haemopurification, 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

On 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 PQ 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 PQ 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 (CKD), chronic liver disease, respiratory failure, chronic obstructive pulmonary disease (COPD), asthma, heart failure, pancreatic disease, acute coronary syndrome (ACS) or stoke. (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 randomisation and concealment

All participants would be randomly stratified into three blocks according to the result of urine dithionite test, that is, light blue, navy blue and dark blue. Block length is set at 12. With the help of SAS V.9.3, patients in different blocks would be allocated to four groups, namely the HD group, HP group, concurrent 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

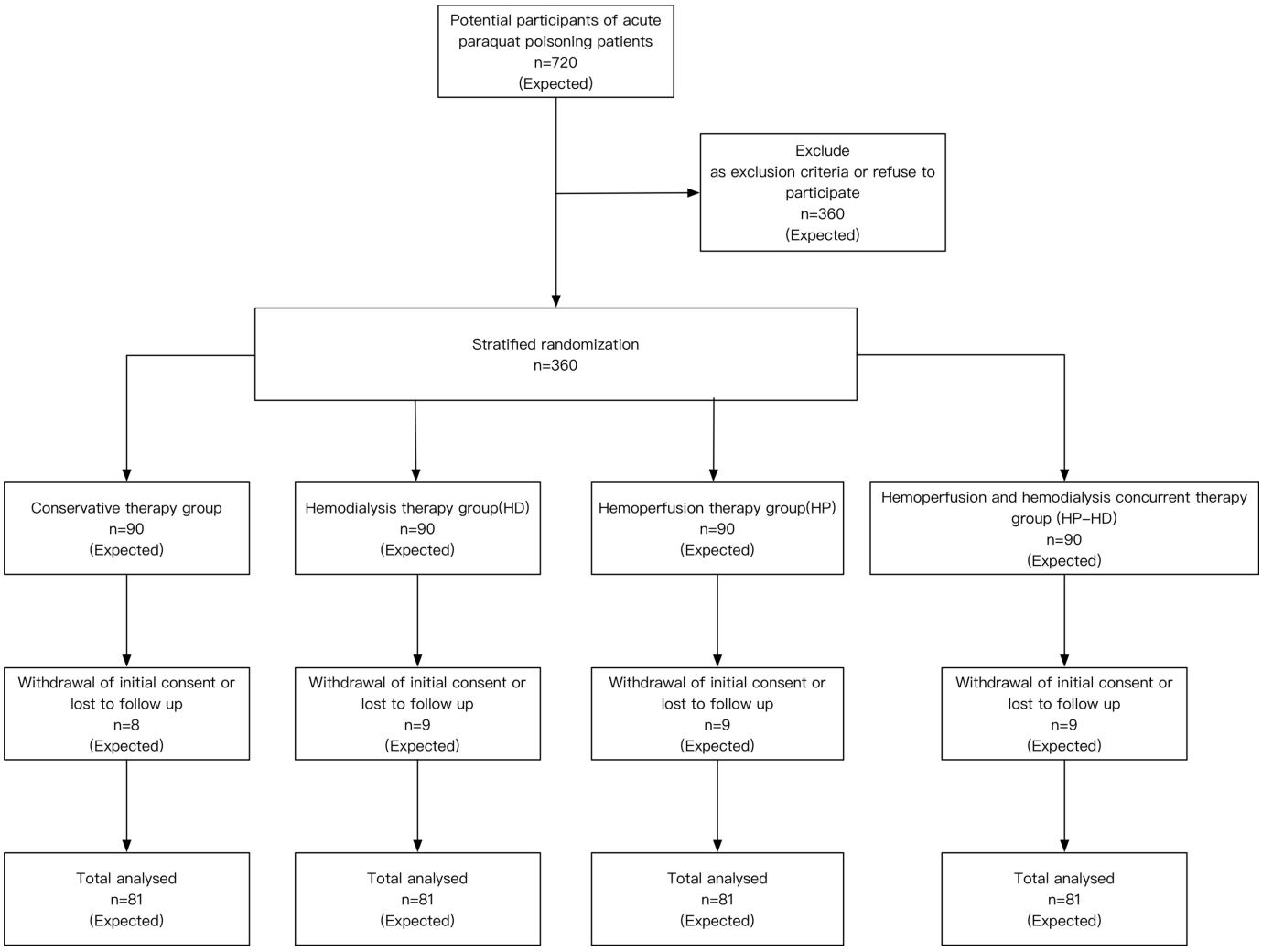

Figure 1 Diagram of the protocol (planned).

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, HP alone, HD alone, and HP–HD concurrent therapy under the Guideline of Chinese Blood Purification for Acute Paraquat Poisoning Patients.[26]

Study procedure

Physicians involved in the study would receive standardised training in carrying out this trial. On enrolment, 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 one mouthful for men=28 mL.[27] PQ ingestion amount, defined as PQ concentration×PQ ingestion volume, would be calculated. Physicians would also assess the

Table 1 The form of basic demographic information and collateral history

Patient ID number	Date	Patient name	Age	Gender	Time of ingestion (to nearest minute)	PQ ingestion volume (mL)	Concentration of PQ (%)	PQ ingestion amount	Source of information	Recording physician

PQ, paraquat.

Table 2 The form of initial assessment

Patient ID number
Date
Group
Time to intervention
Urine test result
Complete blood count
BMI
Smoking history
Alcohol history
Blood gas analysis result
Liver function
Pancreatic function
Kidney function
Blood lactic Acid
Diabetes history
Hypertension history
APACHE II score
Poisoning Severity Score (PSS)

APACHE II, Acute Physiologic and Chronic Health Evaluation; BMI, body mass index.

participants by various scores (table 2), including Acute Physiologic and Chronic Health Evaluation (APACHE II) score and Poisoning Severity Score (PSS).

On suspected diagnosis of PQ poisoning, all patients would receive gastric lavage with room warm water (≥5 L) and 1 g/kg active charcoal via nasogastric tube. After confirmed diagnosis by urine dithionite test, intervention would be initiated on acquisition of informed consent and randomised allocation, which would take less 1 hour 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 of HP HD concurrent therapy for consecutively 3 days.
4. Control group: participants in this group would receive conservative treatment (see below).

According to the Chinese Guideline on Management of Paraquat Poisoning,[11] all patients groups would receive standard treatment as follows. Methylprednisolone 15 mg/kg/day together with cyclophosphamide 15 mg/kg/day 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 40 mm Hg or in case of acute respiratory distress 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 HD machine (Fresenius 4008s. Cartridge: Fresenius Fx60. Both by Fresenius Medical Care AG Co, Germany). Rinse the pipeline with 1 L 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 HD.
3. Therapy and surveillance: connect the pipeline to the catheter, and run the dialysis machine at a speed (mL/min) four times as the patient's weight (kg). Dialysis solution speed should be set at 500 mL/min. Run HD for 4 hours; meanwhile, closely monitor the patients' vital signs. During HD, anticoagulation function should be monitored by transmembrane pressure (TMP) of dialyser. If TMP >250 mm Hg, 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 HP machine (Jafron model JF-800. Cartridge: HA330. Both by Jafron 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 500 mL 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/hour 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 HP 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 the 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 1 L of NS mixed with 3000 IU heparin at a speed of 100–150 mL/min, followed by 600 mL 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 TMP (keep TMP ≤250 mm Hg).

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. HP cartridge should be changed as soon as any charcoal appears. Patients' virtual signs should be monitored during treatment.

Sample size and study power

The hypothesis of the present trial is that all of the active arms, that is, HP, HD and HP–HD concurrent therapy, have a lower mortality compared with conservative therapy in PQ poisoning treatment. Based on this assumption, we searched on several databases, that is, PubMed, EMBASE, SCI, Wanfang Data and CNKI, and found no research had compared HP, HD, HP–HD and conservative therapy for PQ poisoning in one trial; hence, data from different studies are adopted for sample size calculation. Studies of bigger sample size and those that have a similar design to our research are preferentially selected for reference. Gao *et al* compared HP (n=458) and HP+ Continuous Veno-Venous Hemofiltration (CVVH) (n=226) in PQ poisoning treatment, and reported that the mortality of HP was 57.4%.[19] Park and colleagues investigated the efficacy of HP–HD consecutive therapy (n=347) and concurrent therapy (n=383) and found that HP–HD concurrent therapy had a lower mortality (57.9% vs 81.8%).[28] In a Chinese study by Liu *et al*, the mortality of conservative therapy for PQ poisoned patients was 78.2% (n=87).[29] Even less evidence could be obtained in HD treatment for PQ poisoning in the last 30 years. Proudfoot *et al* investigated the efficacy of HD in clearing PQ, but since both HD and peritoneal dialysis were included in the active arm,[30] it is not considered for sample size estimation. Eventually a Chinese study by Yang[31] is adopted, and they concluded that mortality of HD was as low as 38.10% (n=26), as compared with 88.24% in the control group (n=17). Though the absolute sample size was small, it is the largest that we could find, and the investigated intervention did not include peritoneal dialysis; thus, it is selected for reference.

With the 28-day mortality being the primary outcome, and $p<0.05$ defined as significantly different, the Z test with pooled variance[32–36] is applied to calculate the sample size (study power 80%). Based on these data, at least 78, 13 and 81 subjects would be needed for HP, HD and HP–HD group, respectively. As the subjects in each group is set at a 1:1:1:1 ratio, a sample size of 81 per group is adopted. With an estimated dropout rate of 10%, 90 patients would be enrolled for each group eventually.

Monitoring

Arterial blood gas test, complete blood count, coagulation function test, liver function and pancreatic function would be performed and urine volume would be taken every day before haemopurification (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.[10] 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.

Outcomes

Twenty-eight-day mortality would be the primary endpoint for this trial, which is a commonly used measurement[19 28 29 31 37] as most death events occur during this period.[11] The result would be presented in terms of percentage and 95% CI.

Secondary outcomes include: (1) survival time (from the time of PQ ingestion to the time of death), all-cause mortality at the 3rd, 7th and 60th days; (2) rate of necessary oxygen uptake and rate of mechanical ventilation; (3) in-hospital length of stay and ICU length of stay; (4) APACHE II score and PSS score; (5) rate of general complications, such as respiratory failure, acute kidney injury (AKI), acute liver failure, pancreas function abnormality and multiple organ failure (MOF); (6) rate of intervention-related complications, such as catheter placement-related complications, thrombocytopenia and deep venous thrombosis; (7) rate of adverse events, which include unexpected death, severe haemorrhage or oedema, unplanned extubation, coagulation in the extracorporeal circulation, blockage of cartridge, incorrect pipe connection, etc. These results would be presented in the form of mean value and 95% CI. (4) would be assessed at admission. (2), (3), (5), (6) and (7) would be recorded during hospitalisation and reviewed by the time of discharge or in-hospital death. Death events would be recorded during hospitalisation. Patients who are discharged would receive a followed-up phone call at the 60th day from PQ intoxication. All death events would be recorded by date to calculate survival time and mortality at 3rd, 7th, 28th and 60th days. For patients who discontinue or change therapy, data would be collected at the termination of assigned treatment.

Patient involvement

No patients were involved in the development of the research questions or the outcome measures, nor were they invited to develop the plans for design, recruitment or conduction of the study. No patients were asked to assess the burden of intervention. The result will not be disseminated to participants or the relevant communities.

Participant timeline

The study would start after the manuscript is accepted, and it is expected to be completed in 3 years or more depending on actual enrolment. The timeline of participant is listed in table 3.

Data collection and management

All participants would be given a study ID, and all information would be saved by study ID in an electronic

Table 3 Participant timeline

	Enrolment	Discharge from hospital	Day 60
Check the inclusion and exclusion criteria	√		
Sign informed consents	√		
Allocation and intervention	√		
Assessment			
Report and fill the case report forms		√	
Survival status		√	√
Follow-up			√

database. All data in this trial would be recorded and saved as electronic case report form (eCRF), kept and managed by the Emergency Department of Peking Union Medical College Hospital. There would be two databases containing information of this trial, one of which (database 1) only contains information of the ID number, name and intervention of each participant, while another (database 2) contains the ID number, grouping information and clinical data of the patient without intervention details. Statisticians only have access to database 2. Frontline physicians would have restricted access only to the data of the patients that they are directly involved with. Database 1 would be managed by an independent person who has no interest of conflict in this study. All of the envelopes given to physicians with assignment information would be preserved and kept in a locker by the chief data manager. All clinical data including adverse events collected during hospitalisation can be obtained from electronic medical record system or paper notes. Contact information of patients and their family members would be required on admission. Information on patient deaths can be obtained from medical records and follow-up calls.

Statistical analysis

Considering the high cost of each participant, intention-to-treat (ITT) analysis would be adopted to fully use the data. Dropout rate, which may increase the bias of ITT analysis, would stay low in this trial with the relatively short course of disease. To obtain a relatively conservative result, the last observation carried forward method would be used to fill up missing and dropout data. The missing data of survival would be carried forward as death, so as to reduce potential treatment effect bias induced by the active arms. Results would be calculated by SAS V.9.3, and $p<0.05$ is defined as statistically significant. The Cox regression model (5% significance level) would be applied to examine the relationship between 28-day mortality and intervention group, PQ ingestion amount, urine dithionite test results, time lapse from intoxication to treatment, age and the acid–base or electrolyte status on admission. For secondary outcome (2), (5), (6) and (7), RxC contingency tables would be used to test the difference of these indicators in four groups. If significant differences are found, Bonferroni test would be performed to find treatment effect differences between each group. As for length of stay and scores, one-way analysis of variance would be applied. Exploratory subgroup analysis would be performed to investigate treatment effect in different patients. Patients would be divided into subgroups by these factors: urine dithionite test result (light blue, navy blue and dark blue), and time from ingestion to treatment (≥4 hours and <4 hours). The survival time of each group would also be analysed with the help of log-rank test, Cox regression and Kaplan-Meier survival curve.

Data monitoring

The data monitoring committee (DMC) consists of three independent physicians and one statistician. It is responsible for regular review of accumulating trial data on efficacy and safety. It can also suggest to trial sponsor and investigator on trial continuation, modification or cessation based on benefit–risk assessment. Every 4 months, the DMC would hold a meeting to review statistical reports presented by Statistical Data Analysis Center, which is composed of a group of statisticians. The DMC would have access to unmasked results on 28-day mortality, survival time, rate of MOF and rate of severe complications. These outcomes would be kept confidential by DMC unless a clear difference is observed among groups and DMC requests trial termination. It would also review the occurrence of serious adverse events, which include unexpected death, severe haemorrhage or oedema, etc. Adverse events would be collected by self-report by physicians and nurses in charge of the subjects on the eCRF system. The DMC would evaluate these events in the meetings and decide if an early end to the trial should be applied. Inter-rater agreement would be assessed by κ analysis.

Definitions

CKD is defined according to Kidney Disease Outcomes Quality Initiative Guideline as damage or decrease of kidney function,[38] which presents as urinary albumin excretion ≥30 mg/day or estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m^2 for 3 months or more.

According to Kidney Disease Improving Global Outcomes classification,[39] AKI is diagnosed in patients who meet any criteria of the following: (1) Increase in serum creatinine ≥0.3 mg/dL in 48 hours. (2) The serum creatinine has increased to more than 1.5 times than baseline within 7 days. (3) The volume of urine is lease than 0.5 mL/kg/hour for 6 hours.

COPD is defined according to the Global Initiative for Chronic Obstructive Lung Disease criteria.[40] Patients whose spirometry result indicates air flow limitation (forced expiratory volume in 1 s/forced vital capacity <0.7) after bronchodilator inhalation without alternative

explanation for patients' symptoms can be diagnosed as COPD.

Respiratory failure can be diagnosed in the patients with an arterial oxygen PaO_2 <60 mm Hg in air pressure of sea level, with or without $PaCO_2$ >50 mm Hg.

Chronic liver disease is defined as disease of the liver lasting longer than 6 months. Cirrhosis, chronic liver inflammation caused by infection or autoimmune disease are included in chronic liver disease. Cirrhosis is defined according the National Institute for Health and Care Excellence 2016 guideline,[41] in which patients can be diagnosed with cirrhosis with typical imaging, laboratory results together with risk factors or with biopsy confirmation alone.

Acute liver failure is defined as acute damage in liver function without obvious history of liver disease or cirrhosis within 26 weeks. Patients who meet all the following criteria can be diagnosed as acute liver failure[42]: elevated aminotransferases, mental alteration (hepatic encephalopathy) and INR (international normalised ratio) ≥1.5.

ACS is associated with myocardial ischaemia, which includes ST elevation myocardial infarction (STEMI), unstable angina (UA) and non-STEMI (NSTEMI).

ARDS is defined according to Berlin definition.[43] Patients who meet all the criteria below can be diagnosed with ARDS: (1) The respiratory symptoms must occur within 1 week of noticed clinical disease, or patients' present new symptoms or respiratory symptoms in 1 week. (2) Chest X- ray or CT shows signs of pneumonoedema in both sides of lungs which cannot be fully explained by pleural effusion, atelectasis, lobe collapse or pulmonary nodules. (3) Heart failure and fluid overload cannot completely explain the respiratory failure. (4) The patient must present with moderate to severe oxygen impairment which can be defined by the ratio of PaO_2/FiO_2. When the positive end-expiratory pressure (PEEP) is set as 5 cmH_2O or more, the PaO_2/FiO_2 is less than 300 mm Hg.

Abnormal pancreatic function is defined as serum amylase >220 U/L, which can be classified into two degrees, mildly elevated (220–660 U/L) and elevated (>660 U/L).[20]

Multiorgan dysfunction is defined according to the Sepsis-3 definition: patients with Sequential Organ Failure Assessment (SOFA) score ≥2 are determined to have multiorgan dysfunction or MOF.[44]

Ethics and dissemination

If important modifications or decision are made, the Ethics Committee of the First Affiliated Hospital of Zhengzhou University would be informed, and new protocols would be uploaded to Clinicaltrials.gov.

All eligible participants and their family members would be given informed consent documents with adequate time to consider and communicate with physicians. Consent provisions for collection and use of participant data and biological specimens in potential ancillary studies are also included in the informed consent. Refusal to participate in this trial would not influence the care they receive under any circumstances. Discontinuation or modification of treatment could be requested by patients and their families, or in cases of allergic responses to haemopurification materials. Serious events and unexpected adverse events would be recorded and reported to the Ethics Committee of the First Affiliated Hospital of Zhengzhou University and DMC. An independent audit would be held every 6 months to supervise trial conduct. Three toxicologists and three independent statisticians would be invited to the audit. Personal contact information would be accessible only to the research team members who are in charge of follow-up. Full protocol would be accessible to the public on BMJ Open. The results of the present study would be published in international peer-reviewed journals. Original research data could be requested from the corresponding author.

Contributors YL, Y-XG, XY and HZ raised the idea and developed the plan for the trial. YL and Y-XG formulated the intervention plan. J-WC and YX wrote the original paper. J-WC, YX, XL, SY and YM collected the reference data for the trial and designed the case report form (CRF). Y-XG, YW, DY, LC and PS prepared the documents for ethical review and obtained the research ethical approvals. SG revised the paper and work in English. MW reviewed the reference data, calculated the sample size and helped design the analysis plan. YL reviewed and embellished the original paper, and confirmed the final protocol. All authors reviewed the final version of manuscript.

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Competing interests None declared.

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