Time-dependent haemoperfusion after acute paraquat poisoning

Hao-Ru Wang, Jian Pan, An-Dong Shang & Yuan-Qiang Lu

Early haemoperfusion (HP) therapy has been found to be very effective in acute paraquat (PQ) poisoning, but the effective rescue window is still uncertain. Demographic data and the type of therapies administered of 621 patients were included as confounding factors in this retrospective study. After receiver operating characteristic curve analysis and intra-group/subgroup analysis, the initiation of glucocorticoid therapy within 3 hrs of exposure with a second treatment given <21 hrs after exposure, HP initiated within 4 hrs of exposure with a second treatment given <20 hrs after exposure, the appearance of pulmonary lesions ≤8 days after exposure and six other variables were used in a multiple analysis. The strength of positivity of the PQ urine test on admission, HP initiated within 4 hrs of exposure with a second treatment given <20 hrs after exposure, the appearance of pulmonary lesions ≤8 days after exposure, and stage III AKI on admission were used in a multiple analysis. The strength of positivity of the PQ urine test on admission, HP initiated within 4 hrs of exposure with a second treatment given <20 hrs after exposure, the appearance of pulmonary lesions ≤8 days after exposure, and stage III AKI on admission were used in a multiple analysis. The strength of positivity of the PQ urine test on admission, HP initiated within 4 hrs of exposure with a second treatment given <20 hrs after exposure, the appearance of pulmonary lesions ≤8 days after exposure, and stage III AKI on admission were used in a multiple analysis. The strength of positivity of the PQ urine test on admission, HP initiated within 4 hrs of exposure with a second treatment given <20 hrs after exposure, the appearance of pulmonary lesions ≤8 days after exposure, and stage III AKI on admission were used in a multiple analysis. The strength of positivity of the PQ urine test on admission, HP initiated within 4 hrs of exposure with a second treatment given <20 hrs after exposure, the appearance of pulmonary lesions ≤8 days after exposure, and stage III AKI on admission were used in a multiple analysis.
There were significant differences in the survival rate based on the number of positive PQ semiquantitative urine tests (positive result at admission: $\chi^2 = 2.736, P = 0.036$; positive results at admission and first repeat test: $\chi^2 = 3.108, P = 0.031$; all three positive results: $\chi^2 = 3.452, P = 0.022$), the arrival type (survival rate of group A, B and C were 53.07%, 51.96%, and 48.65%, respectively, $\chi^2 = 13.152, P = 0.008$), a medical history of chronic obstructive pulmonary disease (COPD) or asthma ($\chi^2 = 3.112, P = 0.043$; $\chi^2 = 2.964, P = 0.048$), a medication history positive for immunosuppressive drugs ($\chi^2 = 3.685, P = 0.026$), serum creatinine on admission ($t = 3.701, P = 0.045$) and acute kidney injury (AKI) stage I, II or III ($\chi^2 = 13.152, P = 0.008$). Glucocorticoids, immunosuppressors and HP were used a median of 7, 8 and 10 times, respectively. No significant difference was found between the survival rate and the number of repeated treatments ($\chi^2 = 0.008$). Semiquantitative urine tests were conducted 8 times/10 days (range 7–16 days). It was first tested on admission, and testing was repeated after glucocorticoid or immunosuppression therapy. In addition, no significant difference in survival rate was found between age, gender, and other demographic data.

The time after PQ poisoning was considered in further analysis. Patients reached our institute at a mean time of 5.84 ± 2.37 hrs. The mean time of groups A, B and C were found to have a significant difference (2.95 ± 1.96 hrs for the first test, 10.97 ± 3.45 hrs for the second test and 17.24 ± 4.06 hrs for the third test. Gastric lavage, cathartics, and emetics were used only once; the mean time to each treatment was 2.46 ± 2.18 hrs, 3.28 ± 3.02 hrs and 1.54 ± 1.17 hrs, respectively. A significant difference was found in the first appearance of AKI stage I ($P = 0.036$), the first appearance of pulmonary lesions ($P = 0.024$), the first use of glucocorticoids ($P = 0.043$), and the first and second uses of HP ($P = 0.033$) (Table 2). No significant difference was found between patient survival and patient death for the mean time to gastric lavage ($P = 0.106$), cathartic administration ($P = 0.173$), or emetic administration ($P = 0.152$). Additionally, no significant correlation was found between survival rate and the time to gastric lavage (Pearson’s correlation $= 1.203, P = 0.091$).

### Table 1. Demography data and univariate analysis between survival and death patients. Group A: Patients were directly taken to our institute. Group B: Patients were transferred to us after first aid. Group C: Patients were transferred from more than one hospital. COPD: chronic obstructive pulmonary disease. DM: diabetes mellitus.

| Variables                        | Survival Patients (numbers/mean ± SD) | $\chi^2$ value | $P$ value |
|----------------------------------|--------------------------------------|----------------|-----------|
| Age (years)                      | 34.82 ± 10.23                        | 1.024          | 0.121     |
| Gender (Male/Female)             | 159/168                              | 2.156          | 0.113     |
| Medical history (Y/N)            | 142/185                              | 2.417          | 0.108     |
| Hypertension                     | 53/69                                | 2.325          | 0.112     |
| Asthma                           | 8/21                                 | 2.964          | 0.048     |
| COPD                             | 12/35                                | 3.112          | 0.043     |
| Bronchiectasis                   | 9/17                                 | 2.318          | 0.120     |
| Coronary heart disease           | 38/79                                | 1.321          | 0.316     |
| DM                               | 11/26                                | 0.954          | 0.393     |
| Congenital heart disease         | 6/12                                 | 1.021          | 0.112     |
| Tumor                            | 5/7                                  | 0.527          | 0.931     |
| Medication history               | 63/264                               | 2.376          | 0.137     |
| Glucocorticoid                   | 12/26                                | 1.853          | 0.115     |
| Immunosuppressive drugs          | 3/8                                  | 3.685          | 0.026     |
| Bronchodilators                  | 14/22                                | 3.225          | 0.351     |
| Anticoagulants                   | 34/49                                | 1.014          | 0.462     |
| Semi-quantitative of PQ level at admission |                     |                |           |
| +                                | 168/124                              | 2.736          | 0.036     |
| ++                               | 133/118                              |                |           |
| +++                              | 26/52                                |                |           |
| Gastric lavage (Y/N)             | 249/78                               | 1.051          | 0.423     |
| Cathartic (Y/N)                  | 169/158                              | 0.825          | 0.781     |
| Emetic (Y/N)                     | 49/278                               | 1.437          | 0.165     |
| Pulmonary lesions (Y/N)          | 127/200                              | 2.225          | 0.041     |
| Serum creatinine at admission (mg/dL) | 0.76 ± 0.19                        | 1.01 ± 0.17    | 3.701     | 0.045     |
The glucocorticoid variable was divided into two groups, \( \chi^2 \) between survival rate and repeated therapy administrations (number of glucocorticoid treatments: corticoids were the only therapy given before transfer to our institute. No significant difference was found

cathartic administration (Pearson's correlation = 0.357, \( P = 0.114 \)) or emetic administration (Pearson's correlation = 0.211, \( P = 0.285 \)).

Glucocorticoid therapy, immunosuppression therapy and HP were provided approximately once daily; glucocorticoids were the only therapy given before transfer to our institute. No significant difference was found between survival rate and repeated therapy administrations (number of glucocorticoid treatments: \( \chi^2 = 0.871, P = 0.135 \), number of immunosuppressor treatments: \( \chi^2 = 0.914, P = 0.248 \), times of HP: \( \chi^2 = 1.014, P = 0.102 \)). Therefore, the variables were expressed in terms of hours (hours of glucocorticoid therapy: TG1 to TG7, hours of immunosuppressor therapy: TI1 to TI8, hours of HP: TH1 to TH10) and used as dummy variables (Table 2).

For those with a first appearance of stage I AKI, the number of pulmonary lesions present was significantly different in cases of survival and cases of death. A significant difference was also found in patient survival and patient death between the first, second and third administration times of both glucocorticoids and HP. After receiver operating characteristic (ROC) curve analysis, the cut-off time between patient survival and patient death between the first, second and third administration times of both glucocorticoids and HP was 3.18 hrs (rounded to 3 hrs), 3.91 hrs (rounded to 4 hrs), respectively, as shown in Fig. 1. The glucocorticoid variable of was divided into two groups,
≤3 hrs and >3 hrs (survival rates were 55.24% and 51.05%, respectively). The HP variable was also divided into two groups, <4 hrs and ≥4 hrs (survival rates were 59.82% and 48.65%, respectively). A significant difference after the second glucocorticoid treatment was found in the ≤3 hrs subgroup (mean time of patient survival 28.29 ± 6.73 hrs versus 32.17 ± 8.25 hrs, t = 2.814, P = 0.048) but not in the >3 hrs subgroup (31.16 ± 8.39 hrs versus 35.04 ± 9.67 hrs, t = 2.016, P = 0.079). In addition, a significant difference after the second HP treatment was found in the <4 hrs subgroup (31.52 ± 7.90 hrs versus 36.12 ± 6.71 hrs, t = 3.791, P = 0.023) and in the ≥4 hrs subgroup (37.52 ± 8.53 hrs versus 46.12 ± 9.26 hrs, t = 2.868, P = 0.045). No significant difference was found in the time of the second immunosuppressor treatment (28.32 ± 2.34 hrs versus 33.19 ± 4.81 hrs, t = 5.261, P = 0.39).

After ROC curve analysis, the cut-off for the second glucocorticoid treatment was 20.82 hrs (rounded to 21 hrs) in the ≤3 hrs subgroup, and the cut-off for the second HP treatment was 19.87 hrs (rounded to 20 hrs) in the <4 hrs subgroup and 23.26 hrs (rounded to 23 hrs) in the >4 hrs group. The glucocorticoid variable of was divided into three groups: (i) first treatment ≤3 hrs, second treatment <21 hrs, (ii) first treatment ≤3 hrs, second treatment ≥21 hrs and (iii) first treatment >3 hrs (survival rates were 56.16%, 53.69% and 51.05%, respectively). The HP variable was divided into four groups: (i) first treatment <4 hrs with second treatment <20 hrs, (ii) first treatment <4 hrs with second treatment ≥20 hrs, (iii) first treatment ≥4 hrs with second treatment <23 hrs and (iv) first treatment ≥4 hrs with second treatment ≥23 hrs (survival rates were 60.27%, 57.24%, 51.18 and 47.23%, respectively). No significant difference between patient survival and patient death was found in either of these subgroups or in other time periods of glucocorticoid, immunosuppressor or HP treatment (all P > 0.05).

After multiple logistic regression analysis, we found the independent risk factors were semiquantitative urine PQ test level on admission (P = 0.023), semiquantitative urine PQ test level of + + + on admission (P = 0.003), first HP <4 hrs with second HP <20 hrs (P = 0.003), and first appearance of pulmonary lesions ≤8 days (P = 0.047) (Table 3). The ratio of survival rates between the first and second HP treatments was 1.6 versus 1.

**Discussion**

This study found that lower urine dithionite PQ and a time to first HP treatment of <4 hrs with a time to second treatment of <20 hrs were independent predictors for PQ poisoning survival. Earlier studies identified significant prognostic factors such as age, the amount of PQ ingested, plasma PQ concentration, and renal function. Reliable predictors of prognosis would be helpful in guiding therapy. Previous studies considered plasma PQ concentration to be a marker of severity and prognosis. However, none of these as yet alter clinical management; they are all time-dependent prediction methods. In this study, we were able to elucidate the potential benefit of providing treatment in a finite period instead of relying on predictions.

Severe secondary AKI occurred in approximately 50% of cases of PQ intoxication. The key to managing AKI is ensuring adequate renal perfusion by achieving and maintaining haemodynamic stability while avoiding hypovolemia. Studies had suggested that performing the initial HP before the PQ level reached its peak would be the most effective way of eliminating PQ from the body, noting that the plasma PQ level usually peaks within one hour of PQ ingestion. A research study revealed that early HP after PQ exposure might be effective in reducing mortality. However, we were not sure if HP performed within one hour of ingestion would be more helpful since there were almost no patients who arrived within that time period. Despite the fact that the urine dithionite PQ test has low sensitivity, it is still a useful bedside screening tool for PQ intoxication because of its convenience and reproducibility. It was also found that the time to achieve a negative urine dithionite test is a reliable marker for reproducibility.
led to aspiration, asphyxia or mediastinal perforation25, 26. However, no direct complication attributable to gastric activated charcoal in PQ poisoning is still needed. Adverse effects of gastric lavage have been reported—it may have charcoal in PQ poisoning has not been reported in the literature; further study to assess the effectiveness of acti-
manner.

study is needed to ensure the rescue window will last longer if first aid is performed correctly and in a timely
dow defined as a time to first use within 4 hrs of PQ intoxication. The sooner the treatment the better. Further
further study is required to ascertain the specific effects of these techniques in cases of PQ poisoning.
be influenced by the level of oxidative stress in patients, and this was not estimated in this study. Third, although
PQ concentration after HP . In addition, the effect of this change on the survival rate is unknown. Second, HP may
be available. Medical management with gastrointestinal decontamination techniques, methods to increase poi-
son elimination, proper hydration and supportive management are the most important factors in the survival
syndrome, and improve the survival of patients poisoned with organophosphorus pesticides13. Similarly, continu-
lavage was found in our study.

predicting mortality21. We could not identify the exact amount of time required for the semiquantitative urine
test to turn negative since there was no further testing after treatment. We presumed that patients would achieve
a negative test sooner if HP was performed for first time < 4 hrs after ingestion with the second treatment given
< 40 hrs post ingestion. The second HP might be helpful in eliminating the catabolite produced by oxygen free
radical damage.
The key to rescue therapy is the time to administration of appropriate therapy when there is no specific anti-
dote available. Medical management with gastrointestinal decontamination techniques, methods to increase poi-
son elimination, proper hydration and supportive management are the most important factors in the survival
rate in cases of PQ poisoning22. The sooner gastrointestinal decontamination is performed, the better is the out-
come23. A beneficial effect was found when gastric lavage was performed < 4 hrs post ingestion, but it appeared
to adversely affect the outcome if performed more than 4 hrs post exposure5. Activated charcoal seemed useful
in the early stages of acute self-poisoning, but no substantiating evidence has been found24. The use of activated
charcoal in PQ poisoning has not been reported in the literature; further study to assess the effectiveness of acti-
vated charcoal in PQ poisoning is still needed. Adverse effects of gastric lavage have been reported—it may have
led to aspiration, asphyxia or mediastinal perforation25, 26. However, no direct complication attributable to gastric
lavage was found in our study.

On-line high-volume HP can rapidly clear inflammatory cytokines, reduce systemic inflammatory response
syndrome, and improve the survival of patients poisoned with organophosphorus pesticides21. Similarly, continu-
sus venovenous haemodiafiltration was successfully used in the rescue of a patient with a high dose PQ exposure
of 36.48 mg/kg21. Thus, more patients might be saved if PQ elimination or renal replacement therapy can be more
efficiently administered a short time after poisoning.
There were several limitations to this study. First, it was not possible to obtain measurements of the change in
PQ concentration after HP. In addition, the effect of this change on the survival rate is unknown. Second, HP may
be influenced by the level of oxidative stress in patients, and this was not estimated in this study. Third, although
various renal replacement techniques have been shown to improve outcomes for patients with severe poisoning,
further study is required to ascertain the specific effects of these techniques in cases of PQ poisoning.
Overall, the effectiveness of HP therapy in PQ poisoning was time dependent and helpful in the rescue win-
dow defined as a time to first use within 4 hrs of exposure and a time to second use within 20 hrs. Moreover, the
crucial factor was processing HP within 4 hrs of PQ intoxication. The sooner the treatment the better. Further
study is needed to ensure the rescue window will last longer if first aid is performed correctly and in a timely
manner.

Methods
We collected data on patients with PQ poisoning treated at our institute between May 2002 and April 2012. The
inclusion criteria included adulthood (18 years and over) and positive PQ urine semiquantitative test. The exclu-
sion criteria were age less than 18 years of age, lost to follow-up, suspected cases ruled out (all three PQ urine

| Variables                                  | B    | Std. Coefficients | Std. Error | t value | P value |
|--------------------------------------------|------|-------------------|------------|---------|---------|
| Semiquantitative of PQ level at admission  |      | -0.067            | -0.141     | 0.029   | 2.292   | 0.023   |
|                                            | + +  |                   |            |         |         |         |
|                                            | + + +|                   |            |         |         |         |
| Arrival type                               |      | -0.084            | -0.211     | 0.023   | -3.645  | 0.001   |
| Group B                                    |      | -0.023            | -0.053     | 0.021   | 1.306   | 0.193   |
| Group C                                    |      | -0.024            | -0.075     | 0.030   | 0.930   | 0.353   |
| Medication history of asthma (Y/N)         |      | -0.029            | -0.094     | 0.019   | -1.669  | 0.096   |
| Medication history of COPD (Y/N)           |      | -0.059            | -0.102     | 0.017   | -1.857  | 0.082   |
| Medication history of Immunosuppressive drugs (Y/N) | 0.055 | 0.085             | 0.037      | 1.495   | 0.136   |
| Pulmonary lesions                          |      |                   |            |         |         |         |
| The first appearance > 8 days              |      | -0.232            | -0.318     | 0.104   | 1.015   | 0.055   |
| The first appearance ≤ 8 days              |      | -0.133            | -0.274     | 0.085   | 1.457   | 0.047   |
| Haemoperfusion first time < 4 hrs          |      | -0.138            | -0.357     | 0.023   | -7.354  | 0.004   |
| with second time < 20 hrs                  |      |                   |            |         |         |         |
| Glucocorticoid used first time < 3 hrs     |      | -0.113            | -0.125     | 0.022   | -1.495  | 0.127   |
| with second time < 21 hrs                  |      |                   |            |         |         |         |
| AKI at admission                           |      |                   |            |         |         |         |
| Stage II                                   |      | -0.048            | -0.105     | 0.022   | 1.608   | 0.054   |
| Stage III                                  |      | -0.072            | -0.172     | 0.054   | 2.213   | 0.028   |

Table 3. Multiple logistic regression analysis to identify independent factors of HP therapy survival probability. AKI: Acute kidney injury. HP: haemoperfusion. Group B: Patients were transferred to us after first aid. Group C: Patients were transferred from more than one hospital.
Semiquantitative tests were negative), unknown time of exposure, and discharge within 24 hrs without any further treatment. The patient flowchart and the study protocol are shown in Fig. 2.

All dependent variables and subgroups were determined by univariate analysis. Subgroups contained the therapies provided each hour and the number times each therapy was repeated. The data analysis included arrival time (directly arrived or transferred), age, gender, medical history [diabetes mellitus, hypertension, coronary heart disease, congenital heart disease, COPD, asthma and tumour], medication history longer than 6 months (glucocorticoid, immunosuppressive drugs, bronchodilators, anticoagulants), semiquantitative urine dithionite PQ test results (the first test was performed on admission; subsequent tests were given at 6-hr intervals, normally 3–4 times), gastrointestinal decontamination (gastric lavage, cathartic administration, and emetic administration), use of glucocorticoids and immunosuppressive drugs, HP (average reinfusion rate was 9 L/session and 300 mL/min in the postdilution mode), serum creatinine (the first blood test was performed on admission, tested daily for the first 3 days and then tested at 1- to 2-day intervals), and pulmonary lesions. Changes in serum creatinine level categorized AKI into three stages (increase ≤0.3 mg/dL, 0.3–4 mg/dL and ≥4 mg/dL). Pulmonary lesions were diagnosed by characteristic effusion and fibrosis in computed tomography (CT) images (the first CT scan was performed on admission, subsequent CT scans were performed at 2- to 3-day intervals). The number of times each therapy was repeated, the frequency of outcome measurements, and the rescue window after PQ poisoning were assessed in hours.

Student’s t test or a Wilcoxon rank-sum test was performed on numerical data among groups. The chi-square test was used for categorical data. Pearson correlation analysis or curve estimation was used to estimate correlations between two variables. Repeated-measures analysis of variance was used to estimate the relationship between repeated therapies and the tests. ROC curve analysis was used to evaluate the threshold value.
of numerical variables, which were then transformed into binary variables. A one-way analysis of variance or Kruskal-Wallis test was used to compare multiple subgroups; otherwise, subgroups were divided into dummy variables and analysed by univariate analysis. The variables with P values less than or equal to 0.10 were used in the multiple-factor analysis. Multiple logistic regression analysis was used to evaluate the relationship between dependent variables and survival probability. The level of statistical significance was set at P < 0.05. All analyses were performed using SPSS software (version 13.0, SPSS Inc., IBM, Chicago, IL, USA).

This study was approved by the Ethical Committee of the First Affiliated Hospital, School of Medicine, Zhejiang University. We obtained the verbal consent of all patients or their relatives by phone calls.

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Author Contributions

Y.Q.L. conceived and designed the experiments. H.R.W., J.P. and A.D.S. performed the treatments and collected data. H.R.W. analyzed the data. Y.Q.L. and H.R.W. contributed to the writing of the manuscript. All authors reviewed the manuscript.

Additional Information

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