

Original Article

Implication of PVPI and EVLWi in prognostic evaluation of acute paraquat poisoning

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Abstract: To analyze the correlation between the hemodynamic parameters pulmonary vascular permeability index (PVPI) and extravascular lung water index (EVLWi), and serum paraquat concentration in poisoned patients. Additionally, we set out to investigate their indications in prognostic evaluation of acute paraquat poisoning. A total of 45 paraquat poisoning patients from March 2014 to December 2016 were recruited. All patients received gastric lavage plus strengthened blood purification therapy. Non-invasive hemodynamic monitoring was performed to measure PVPI and EVLWi. Serum paraquat concentration was examined to calculate clearance rate by purification. Hemodynamic indexes were compared between survival and death groups to analyze their prognostic indications. Among all 45 patients who orally ingested 44.2 ± 10.3 ml paraquat, 18 of them (40.0%) were deceased, and showed significantly higher serum paraquat, poisoning time, volume plus higher PVPI and EVLWi than those in the survival group ($p < 0.05$). After paraquat poisoning, PVPI and EVLWi showed dynamic changes. The 2-5 d survival group showed lower PVPI or EVLWi than death group ($p < 0.05$). In the survival group, serum paraquat showed higher decreasing velocity than in the death group ($p < 0.05$). ROC analysis found higher value of EVLWi combined with PVPI in differential diagnosis of the end-point (AUC = 0.936). After blood purification, serum paraquat, PVPI, and EVLWi all significantly decreased. The overall curative rate of 45 patients receiving blood purification was 60.00%. PVPI and EVLWi have certain implications in prognostic evaluation of acute paraquat poisoning patients. Strengthened blood purification can decrease serum paraquat concentration and improve curative rate.

Keywords: Paraquat poisoning, strengthened blood purification, EVLWi, PVPI

Introduction

Paraquat is highly poisonous and lacks specific antidotes. It can be absorbed by the body via skin, digestive tract, airway, and is widely distributed among certain body tissues and organs [1-3]. Oral ingestion of paraquat has relatively fast absorption and slow excretion, although some poisoning patients show mild early symptoms. Blood purification and immune therapy have gained certain efficiency in the clinic, but overall treatment and prognosis were relatively poor, and mortality rate is around 50% [4, 5]. Therefore, identification of an effective monitoring index can benefit disease evaluation, diagnosis, and treatment. Lung is the major target organ of paraquat, and acute alveolitis can occur secondary to paraquat poisoning. Non-invasive hemodynamic monitoring can calculate pulmonary vascular permeability index (PVPI) and extravascular lung water index

(EVLWi), which can quantify pathological features of pulmonary edema and permeability of pulmonary micro vessels, thus predicting lung injury condition. Prognosis of paraquat poisoning patients is directly correlated with blood paraquat concentration, and the re-rise of serum paraquat after whole blood perfusion may be related with unfavorable prognosis [6]. This study investigated hemodynamic parameters PVPI and EVLWi, and paraquat concentration, for the evaluation of treatment efficiency for blood purification therapy, thus providing references for clinical treatment of paraquat poisoning and prognosis evaluation.

Information and methods

General information of patients

A total of 45 paraquat poisoned patients who were admitted in our hospital from March

Paraquat poisoning indicators

Table 1. General conditions of paraquat poisoning patients

Group	Sex (M/F)	Age (yr)	Poison time (hr)	Poison dose (mL)	Oxygenation (mmHg)	Serum paraquat (mg/L)	Treatment time (h)	Paraquat decrease velocity (mg/Lh)
Survival (n = 27)	12/15	32.4 ± 3.8	3.4 ± 0.6	46.16 ± 6.06	305.4 ± 101.62	6.73 ± 2.15	4.5 ± 0.5	0.58 ± 0.06
Death (n = 18)	10/8	30.2 ± 3.4	5.5 ± 0.9	81.15 ± 13.13	337.5 ± 103.4	12.44 ± 5.24	5.2 ± 1.5	0.47 ± 0.05
χ^2/t	0.534	1.982	9.410	9.113	1.033	8.235	1.964	6.426
<i>P</i>	0.46	0.06	0.00	0.00	0.31	0.00	0.06	0.00

Table 2. Comparison of hemodynamic indexes among differential prognosis patients on day 5 after treatment

Group	MAP (mmHg)	CVP (mmHg)	HR (per min)	CI (L·min ⁻¹ ·m ⁻²)	SVI (ml/m ²)	EVLWi (ml/kg)	PVPI
Survival (n = 27)	76.52 ± 15.76	10.38 ± 1.61	118 ± 16	4.33 ± 1.08	38.76 ± 5.13	6.83 ± 0.74	1.58 ± 0.52
Death (n = 18)	75.37 ± 12.51	10.52 ± 1.47	121 ± 20	4.52 ± 1.14	37.57 ± 6.25	10.51 ± 1.96	2.33 ± 0.80
<i>t</i>	0.260	0.296	0.557	0.566	0.698	7.612	3.701
<i>P</i>	0.398	0.384	0.290	0.287	0.244	< 0.001	0.001

Note: MAP, mean arterial pressure; CVP, central venous pressure; HR, heart rate; CI, cardiac index; SVI, stroke volume index; PVPI, pulmonary vascular permeability index; EVLWi, extravascular lung water index.

Table 3. Regression logistic analysis of the predictor of death

Factor	β	Wald	<i>P</i>	OR
EVLWi	3.022	6.048	< 0.01	0.048
PVPI	-2.480	9.144	< 0.01	0.209

2014 to December 2016 were recruited. Inclusive criteria: All patients orally ingested paraquat. All participants agreed to monitor hemodynamic using non-invasive approach. No patients had history of basic disease. Exclusive criteria: Age < 15 yrs; Survival time < 1 week; Received blood purification in other hospitals; Complicated with pulmonary or cerebrovascular diseases; Poisoning time > 24 hr; At pregnancy; With gastrointestinal bleeding. This study was approved by the Ethical Committee of our hospital, and all patients or families have signed informed consents.

Treatment approaches

All patients received gastric lavage and enema, before which venous blood was collected for quantitative analysis of paraquat by sodium dithionite. After development and dilution, spectrometry measurement was performed at 400nm. The poisoning time was calculated as the duration between oral ingestion and sample collection. Gastric lavage and enema were performed after blood-gas analysis in artery puncture. All patients received strengthened blood purification, including plasma replacement, blood perfusion, and dialysis. In brief,

blood dialysis cannula was inserted into right femoral vein. Fresh plasma was replaced at 200 ml/d, with perfusion velocity at 2 hours per time, blood volume at 180 ml/min and plasma volume at 40 ml/min, plus dialysis blood volume at 200~300 ml/min and dialysis buffer volume at 500 ml/min. Dialysis was performed 4 hours per time, and strengthened blood dialysis was performed daily within one week. Blood pressure, ECG, heart rate, and SpO₂ were continuously monitored. A BioZ-ICG non-invasive hemodynamic monitoring apparatus was used to measure hemodynamic parameters. Bio-resistant electrodes at the neck and chest skin were applied to measure chest cavity biological resistance, which was then used to calculate hemodynamic parameters. MAP, SVI, EVLWI, and PVPI per pulse were continuously monitored. Then 15 ml cold saline was injected at the cannula with temperature probe at subclavian or internal jugular veins. Three measurements were performed at 900 am, 1400 pm and 1800 pm on each day and were calculated for average values in 5 consecutive days. Patients were assigned into survival and death groups based on prognosis. Hemodynamic parameters were compared between two groups for evaluating the value in prognosis.

Statistical approach

SPSS19.0 software was used for analysis. Comparison of the ratio was performed by Chi-square or corrected Chi-square test. Those

Paraquat poisoning indicators

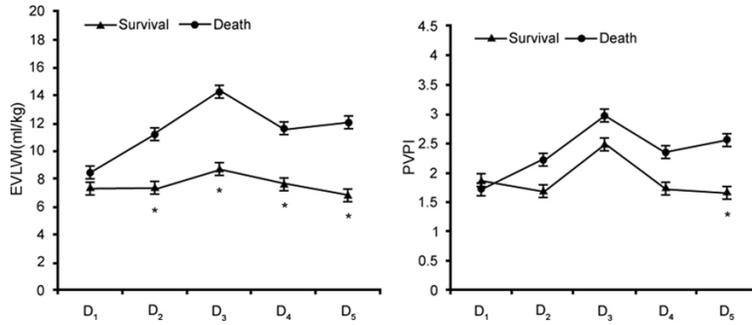


Figure 1. Hemodynamic indexes of survival and death patients. *, $p < 0.05$ compared to the death group.

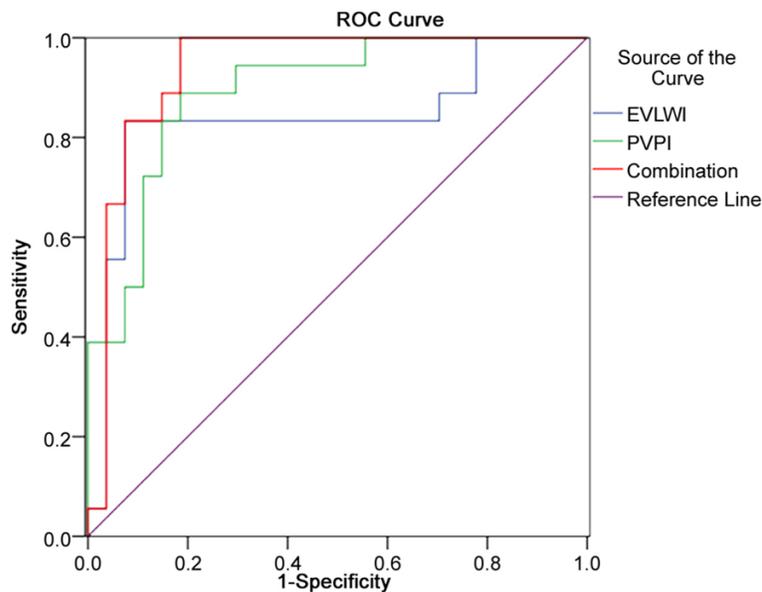


Figure 2. Differential diagnosis value of single or combined EVLWi and/or PVPI on day 5 after treatment.

measurement data fitting a normal distribution are presented as mean \pm standard deviation (SD). Comparison of means was performed by t-test. A statistical significance was defined when $p < 0.05$.

Results

General conditions of paraquat poisoning patients

Among 156 paraquat poisoning patients admitted in our hospital from March 2014 to December 2016, 45 of them were recruited in this study, including 21 males and 24 females, aging between 15 and 65 years (average age = 31.5 ± 4.2 years). All patients orally ingested paraquat, with dosage at 10~78 ml (average =

44.2 ± 10.3 ml). All patients were admitted within 12 hours after paraquat intake. A total of 18 patients died within 28 days, with mortality rate at 40%.

Comparison of general conditions between survival and death groups

No significant difference was found in sex ratio, age, oxygenated index or treatment initiation time between two groups ($p > 0.05$). In the death group, paraquat concentration, poisoning time, and volume were significantly higher than survival group ($p < 0.05$). In the survival group, the decreasing velocity of serum paraquat concentration was higher than that in the death group ($p < 0.05$, **Table 1**).

Comparison of hemodynamic indexes in patients with different prognosis

The survival group patients showed EVLWi and PVPI at 6.83 ± 0.74 ml/kg and 1.58 ± 0.52 , respectively. While the death group showed 10.51 ± 1.06 ml/kg for EVLWi and 2.37 ± 0.80 for PVPI, both of which were significantly lower

than in the death group ($p < 0.05$). No significant difference existed in MAP, CVP or HR between two groups ($p > 0.05$, **Table 2**).

To identify the predictor for death, regression analysis was performed after including EVLWi and PVPI. As shown in **Table 3**, EVLWi and PVPI was the independent risk factor for prediction of death.

Dynamic change of PVPI and EVLWi among patients with different prognosis

A dynamic changing pattern existed for PVPI and EVLWi in paraquat poisoning patients. No significant difference of PVPI or EVLWi was found between 1 day survival group and death group. EVLWi of 2~5 days survival group was

Paraquat poisoning indicators

Table 4. Serum paraquat and hemodynamic concentration before/after blood purification

Group	PQ (mg/L)	MAP (mmHg)	CVP (mmHg)	HR (per min)	CI (L·min ⁻¹ ·m ⁻²)	SVI (ml/m ²)	EVLWi (ml/kg)	PVPI
Before (n = 45)	8.82 ± 3.47	74.32 ± 14.57	10.83 ± 1.58	112 ± 18	4.54 ± 1.13	37.28 ± 5.43	9.31 ± 0.74	1.98 ± 0.63
After (n = 45)	3.86 ± 1.02	75.43 ± 13.15	10.39 ± 1.51	106 ± 21	4.28 ± 1.06	38.67 ± 5.08	7.04 ± 0.86	1.65 ± 0.57
t	9.200	0.379	1.351	1.455	1.126	1.254	13.422	2.606
P	< 0.001	0.353	0.090	0.075	0.132	0.107	< 0.001	0.005

Note: PQ, serum paraquat concentration; MAP, mean arterial pressure; CVP, central venous pressure; HR, heart rate; CI, cardiac index; SVI, stroke volume index; PVPI, pulmonary vascular permeability index; EVLWi, extravascular lung water index.

lower than the death group ($p < 0.05$), and PVPI showed consistent trend with EVLWi, as it gradually increased within 1~3 days, and then sharply decreased at 4 days. The five day survival group showed further decrease of parameters, with re-elevation in death group (**Figure 1**). ROC analysis showed a relatively higher value of EVLWi combined with PVPI in differential diagnosis of death (AUC = 0.936), as it was higher than single EVLWi (AUC = 0.835, sensitivity: 0.42, specificity: 1.825, cutoff value: 0.903) or PVPI on day 5 post treatment (AUC = 0.893, sensitivity: 0.01, specificity: 0.977, cutoff value: 0.05) (**Figure 2**).

Paraquat and hemodynamic indexes before and after blood purification

Before blood purification, serum PQ concentration was 8.82 ± 3.47 mg/L, which was decreased to 2.86 ± 1.02 mg/L with significant decrease ($p < 0.05$). EVLWi and PVPI were 9.31 ± 0.74 ml/kg and 1.98 ± 0.63 before purification, and were 7.04 ± 0.86 ml/kg and 1.65 ± 0.57 after purification, with significant decrease ($p < 0.05$, **Table 4**).

Treatment efficiency evaluation of strengthened blood purification

Among 45 hospitalized patients, 27 survived within 28 days, and 18 died (mortality rate = 40%). The 6-month follow-up on surviving patients showed no significant pulmonary fibrosis under chest CT, no failure of other organs, and normal artery blood-gas analysis. The curative rate of strengthened blood purification for paraquat poisoning was 60%, which was significantly higher than the classical method (10~20%).

Discussion

Paraquat poisoning patients have relatively high mortality rate. Due to low lethal dosage and lack of specific prognostic index in the clinic, early prognostic evaluation of paraquat poi-

soning patients is still difficult. Therefore identification of early predicting parameters for paraquat poisoning severity and prognosis is of critical importance [7-9]. Current approaches mainly use serum paraquat concentration combined with poisoning time to evaluate severity, disease condition, and prognosis of patients. However, due to relatively shorter time window for serum paraquat monitoring, plus high test cost and technical requirement, this assay is still not under wide application. Serum paraquat concentration is correlated with initial lactate level, which can thus reflect poisoning severity of patients and can be used for prognostic evaluation [7, 10, 11]. Paraquat poisoning can lead to acute alveolitis, and the major target organ of paraquat is the lungs. Under enhanced CT, pulmonary damage can be visualized for early evaluation of disease condition [12, 13]. EVLWi and PVPI showed sharp changes even before imaging evidence in acute respiratory distress syndrome (ARDS) patients, and can reflect pulmonary edema condition and sub-type [14-17]. This prospective study observed the role of the hemodynamic index EVLWi and PVPI in prognostic evaluation, in conjunction with the treatment efficiency of strengthened blood purification, thus providing evidence for diagnosis, treatment, and prognostic evaluation of acute paraquat poisoning in the clinic.

Pulmonary mesenchymal fluid and alveolar fluid can directly reflect EVLW, which, however, cannot differentiate origin of pulmonary edema. EVLWi as one dynamic index can directly reflect severity of pulmonary edema [16, 18, 19], while PVPI can differentiate subtype of pulmonary edema [20-22]. In this study, we found significantly higher serum paraquat concentration, poisoning time, and volume in death group than those in survival group, which had higher decreasing velocity of serum paraquat concentration than in the death group, indicting the importance of serum paraquat concentration for patient prognosis. The death group

patients had significantly higher PVPI and EVLWi than the survival group, indicating possible correlation between serum PVPI/EVLWi and prognosis. The monitoring of serum PVPI and EVLWi found that, although dynamic changes existed at 2~5 days, the survival group consistently had lower PVPI and EVLWi than the death group, and serum paraquat concentration, PVPI and EVLWi all significantly decreased after blood purification. All these data suggest more severe alveolar infiltration and mesenchymal damage in the death group. After intake, paraquat mainly enriches in pulmonary tissues, thus even during the phase of decreasing serum paraquat, lung tissues may still have active intake. In this study, EVLWi combined with PVPI had relatively higher differential diagnostic value for death (AUC = 0.936) than single use of EVLWi or PVPI, indicating certain values of clinical application of BioZ-ICG non-invasive hemodynamic monitoring index PVPI and EVLWi in early prognostic evaluation of paraquat poisoning patients, and can work as reference indexes.

The critical point for treatment of paraquat poisoning is rapid clearance of paraquat inside the body to decrease its concentration. As paraquat does not attach onto red blood cells, serum perfusion can remove paraquat, and early-phase serum perfusion is one effective method for clearance of paraquat [23]. Serum replacement can clear multiple pathogenic substances inside serum, and can clear blood paraquat. However, due to the use of large amounts of xenograft plasma, the incidence of blood transfusion complication is rapidly increasing. Plasma perfusion is performed to separate serum with platelet and red blood cells, and absorb toxic components of serum, which is back-transfused into the body, thus optimizing absorption efficiency, and decreasing complication during perfusion treatment [24-26]. This study used strengthened blood purification to treat paraquat poisoning, and obtained 60% curative rate among 45 patients. Some studies showed decreased clearance rate of paraquat by plasma replacement with decreased blood paraquat concentration [27]. We thus further employed blood dialysis treatment on poisoning patients receiving plasma replacement, to optimize the advantage of blood purification. However, due to the poisoning time or dosage, some paraquat poisoning patients still have poor survival, requiring

more clinical trials and optimization of blood purification.

In summary, PVPI and EVLWi have certain implications in prognostic evaluation on acute paraquat poisoning patients. Strengthened blood purification can decrease plasma paraquat concentration and result in higher curative rate than traditional methods.

Disclosure of conflict of interest

None.

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Paraquat poisoning indicators

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