Original Article
Impact of Xuebijing and ulinastatin as assistance for hemoperfusion in treating acute paraquat poisoning

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Abstract: Objective: As the effect of Xuebijing as combined treatment in hemoperfusion (HP) toward acute paraquat (PQ) poisoning is not clear. We retrospectively analyzed 119 cases of acute paraquat poisoning in Tianjin first central hospital; the patients were divided into 3 groups based on treatment. Control (group A) patients underwent standard hemoperfusion with conventional treatment, while the experimental groups combined hemoperfusion with Xuebijing (group B) or ulinastatin (group C). Standard biomedical indicators, such as organ dysfunction and mortality were recorded and compiled, both in short (<7 days) and long (7-28 days) terms. Then, the effect of Xuebijing in combination to the standard (HP) treatment was evaluated by direct comparison. The results showed that using either Xuebijing or ulinastatin as additional treatment to standard HP significantly helped the overall outcomes, as evidenced by lower organ dysfunction and mortality. In addition, Xuebijing (group B) yielded a more pronounced improvement compared with ulinastatin (group C) in combination with HP (All P<0.05). Our findings indicated that both Xuebijing and ulinastatin provided positive impacts on HP treatment toward acute paraquat poisoning, with better outcomes observed with Xuebijing, which should be considered for more frequent use in clinical practice.

Keywords: Hemoperfusion, acute paraquat poisoning, Xuebijing, ulinastatin

Introduction

Acute paraquat poisoning is one of the most common drug poisonings in the clinic, mainly because of the popularity of paraquat in rural and suburban areas, where it is used as an inexpensive and easy-to-handle herbicide. Thus, acute paraquat poisoning has occurred more frequently in recent years due to increasing amounts of paraquat-used in China and its highly fatal side effects. In fact, paraquat has been banned in more than 20 countries. Based to China's FDA regulations, water based paraquat will not be allowed in China, starting from July 1st, 2016. In spite of these protective regulations, acute paraquat poisoning is still one of the most challenging intensive care units (ICU) diseases, due to its acute onset, rapid absorption, high rate of death, and inexistence of specific antidotes.

The toxicological mechanism of paraquat has been well described. In general, paraquat gets into human blood system easily through skin contact, and the respiratory and digestive tracts. Various reactive oxygen species (O_2^-, H_2O_2, and OH^-) produced from paraquat active the human immune system and induce a variety of inflammatory cytokines. Indeed, most early deaths from acute PQ poisoning are caused by multiple organ failure. Because of the special ability for PQ intake, the lung is the most important target organ of PQ poisoning, which progresses to respiratory failure gradually, and results in a motility of 25% to 76% [1].

Currently, there is no specific antidote for acute PQ poisoning. Traditional therapies include gastrolavage, catharsis, diuresis and other symptomatic treatments. Hemoperfusion (HP) has been commonly used in the clinical an effective treatment for early-stage poisoning due to its ability to rapidly adsorb hazardous compounds from blood. However, inflammation is a potential drawback of HP treatment. Thus, ulinastatin is often used to inhibit the inflammatory cytokines. Xuebijing is an intravenous preparation made from five traditional Chinese medicines,

namely Chishao (Radix Paeoniae Rubra), Danggui (Radix Angelica Sinensis), Chuanxiong (Rhizoma Chuanxiong), Honghua (Flos Carthami), and Danshen (Radix Salviae Miltiorrhizae). Xuebijing has been shown in clinical trials to improve the immune system, inhibit the inflammatory response and positively affect SIRS and MODS. Here, we aimed to assess the effects of Xuebijing and ulinastatin as assistance for standard hemoperfusion in treating acute paraquat poisoning.

Patients and methods

Study population

Patients: A total of 119 cases of acute paraquat poisoning diagnosed between March 2012 and March 2014 at the ICU department of the Tianjin First Center Hospital, Tianjin, were analyzed. The inclusion criteria for this study were: (1) clear history of poisoning, with paraquat detected in blood or urine; (2) admission time within 24 h of poisoning and no pre-treatment prior to admission; (3) no history of serious chronic organ disease; (4) no hemoperfusion contraindications. Exclusion criteria were: (1) hospital stay of less than 24 hours or death within 24 hours; (2) presence of other pesticide poisoning; (3) pregnancy. Based on these inclusion and exclusion criteria, a total of 119 patients were enrolled, including 54 males and 65 females. They were 36.8±10.8 (range: 16-77) years old. All patients were diagnosed with oral poisoning with 20% paraquat solution (10-100 ml intake). The admission time from the beginning of poisoning was 1.0-20.5 h, averaging 6.1±3.7 h. All cases were treated with hemoperfusion. Based on treatment type, the patients were divided into three groups: 1) HP treatment only (control group, 37 cases); 2) HP treatment in combination with Xuebijing (43 cases), and; 3) HP treatment in combination with ulinastatin (39 cases). No statistically significant differences were obtained among groups for gender, age, amount of paraquat uptake, admission time, clinical performance and HP treatment. The study protocol was approved by the Institutional Review Board of The First Central Clinical College of Tianjin Medical University, Tianjin, China. Signed informed consents were provided by all patients or their guardians. The treatment and observation time was 28 days, with 90 days random follow-up interviews.

Clinical manifestations and auxiliary examination: Patients all presented digestive tract symptoms at admission, with various degrees of respiratory system, liver, kidney, and heart damage. Total follow-up time was defined as time from date of operation to the last clinical visit or correspondence with the institutional registry. WBC, ALT, Cr, CK-MB, and other parameters were assessed, and PQ concentration was also determined daily. Enhancement CT and chest X-ray were also performed for the diagnosis of pulmonary edema, infection and fibrosis. Pulmonary fibrosis was diagnostic based on TRCT examination showing increased lung packed texture, disorder, and growth of multiple thin strips or grid shadow; in severe cases both lungs turned into a honeycombs.

Therapeutic methods

Conventional treatment: Gastrolavage with 2% $NaHCO_3$, catharsis with 20% mannitol, diuresis and other symptomatic treatments were performed. Multiple rehydration sessions were applied to correct water-electrolyte disturbance. Hormones were used to prevent pulmonary fibrosis as early as possible, and glutathione was utilize to scavenge oxygen free radicals. Antibiotics were used in case of pulmonary infections. To avoid high oxygen concentrations, treatment by oxygen inhalation or ventilator was carried out with PEEP positive pressure ventilation, in case of $PaO_2 < 40$ mmHg or ARDS. In case of renal failure, the patient was given hemodialysis.

Hemoperfusion treatment: The hemoperfusion (HP) treatment was administered after admission through selected internal jugular or femoral vein catheter. Perfusion was conducted with the apparatus and method established by Medical Biological Materials co., Li Zhu LTD (China), the one-time disposable blood perfusion model HA-230. HP was conducted for 2-3 h, once daily, and duration of the hemoperfusion treatment was determined by the blood PQ concentration and clinical characteristics.

Xuebijing treatment: Xuebijing (Tianjin Red Sun Pharmaceutical) intravenous fluids were applied in addition to the hemoperfusion treatment. The amounts administered were 50-100 ml, 1-2 times/day during 7 days; the regimen was tailored to each patient based on vital data.

Table 1. Patients' general information

Group	HP (n=37)	HP + Xuebijing (n=43)	HP + ulinastatin (n=39)
Age	35.25±8.75	33.29±7.66	32.67±11.37
Male	18	19	17
Female	19	24	22
Poisoning level (ml)	33.35±16.49	35.56±8.14	34.25±11.24
PQ conc. (mg/L)	12.26±4.59	11.87±6.63	10.97±9.97
Admission time (h)	12.31±8.21	10.32±6.47	11.98±10.24

Table 2. Fatality times and rates

Group	Death (<7 d)		Death (7-28 d)		Total Death	
	N	Fatality (%)	N	Fatality (%)	N	Fatality (%)
HP (n=37)	19	51.3	7	18.9	26	70.2
HP + Xuebijing (n=43)	9	20.9[a,b]	8	18.6	17	39.59[a,b]
HP + ulinastatin (n=39)	11	28.2[a]	10	25.6	21	53.8[a]

[a]Compared with control group, P<0.05; [b]compare with HP + ulinastatin group: P<0.05.

Table 3. Comparison of patients with pulmonary fibrosis (PF)

Group	Number of patients	PF positive	Percentage
HP (n=37)	37	26	70.2
HP + Xuebijing (n=43)	43	18[a,b]	41.9[a,b]
HP + ulinastatin (n=39)	39	24	61.5

[a]Compared with control group, P<0.05; [b]compare with HP + ulinastatin group: P<0.05.

Ulinastatin treatment: Ulinastatin (Guangdong Temple Biochemical Pharmaceutical co., LTD.) intravenous fluids were applied as addition to the hemoperfusion treatment, at 200 thousands units, twice a day for 7 days.

Statistical analysis

All statistical analyses were performed with SPSS (version 15.0, Chicago, IL, United States). Categorical variables were analyzed by chi-squared test. P<0.05 was considered statistically significant.

Results

Group comparison for general data

As shown in **Table 1**, the three groups of patients were comparable based on gender, age, poison dose, blood PQ concentration at first poisoning, and time from poisoning to first HP. Indeed, there was no statistically significant difference (P>0.05) in any parameter, indicating that the groups are comparable.

Fatality times and rates

Compared with the control group, both the immediate fatality rate (within 7 days) and total death rate were significantly lower in the HP + Xuebijing or HP + ulinastatin groups (P<0.05). Interestingly, HP + Xuebijing treatment resulted in an even higher clinical improvement compared with the HP + ulinastatin group (P<0.05, **Table 2**).

Effect of treatment on pulmonary fibrosis (PF)

It is known that PQ poisoning might cause lung failure, including frosted glass change, exudation, consolidation, fibrosis, mediastinal and subcutaneous emphysema, and pleural effusion. Thus, the lungs of all patients were checked for possible pulmonary fibrosis using CT. The pulmonary fibrosis developed with time and was consistent with progress toward respiratory failure during the clinical progression. As shown in **Table 3**, both Xuebijing and ulinastatin were effective when used as addition to standard HP toward preventing pulmonary fibrosis; interestingly, better results were obtained with Xuebijing.

Clinical parameters in patients during treatment

As shown in **Table 4**, no significant differences were obtained at admission among the three tested groups, for biochemical parameters. With disease progression, the multi-organ damage became a very serious issue. Compared with the control group, Xuebijing and ulinastatin treated individuals showed improved clinical parameters for damage of organs, including lung, heart, liver and other important organs. No significant difference was observed in lung and heart indices between the two experimental groups (Xuebijing or ulinastatin). Interestingly, after 3-day treatment, the Xuebijing group showed a more pronounced improvement in

Table 4. Selected clinical parameters in patients during treatment

Group	Time	PO₂ (mmHg)	CK-MB (U/L)	ALT (U/L)	Cr (umol/L)
HP	0	93.20±11.82	14.30±9.21	45.17±12.33	88.92±21.30
	3 days	69.31±6.32	32.81±12.77	165.77±22.99	195.33±26.88
	7 days	54.92±8.22	38.14±11.27	402.65±20.40	315.49±30.71
HP + Xuebijing	0	92.50±9.11	13.81±10.94	47.20±11.95	89.62±20.58
	3 days	90.12±10.35	17.27±8.52	68.51±22.34	99.80±26.38
	7 days	77.50±14.67	23.52±16.89	102.55±24.21	100.21±5.64
HP + ulinastatin	0	91.27±8.16	14.22±8.59	44.92±11.52	86.38±25.34
	3 days	88.85±10.87	22.74±8.35	99.81±14.54	132.27±22.11
	7 days	74.51±9.66	33.26±11.23	212.44±12.28	216.54±15.89

liver and kidney indices compared with patients treated with ulinastatin.

Discussion

Although paraquat remains a very popular pesticide in China, there is no good antidote for acute paraquat poisoning. In addition, the mechanism of PQ is complicated and not well understood. It has been shown that PQ can cause important tissue damage by oxygen free radicals and lipid peroxidation, which lead to SIRS through multiple cytokines and inflammatory mediators. During acute PQ poisoning, the pulmonary concentrations of PQ may be higher than that of plasma. Therefore, the primary cause of mortality in PQ poisoning is respiratory failure, due to oxidative damage to the alveolar epithelium and subsequent obliterating fibrosis [2, 3]. Pulmonary edema is an early clinical feature of lung damage, and progresses to ARDS rapidly [4-6]. It is critical to develop new clinical methods to further improve patient outcomes.

So far, for PQ treatment, hemoperfusion (HP) [3, 7] has been considered the only effective approach, and has been broadly applied in the clinic. Notably, it has been reported that charcoal HP is effective and should be continuously administered for 6-8 h only if it can be initiated within 2 h of PQ injection, or within 4 h of PQ ingestion. Also, multiple clinical studies have shown that early HP use could reduce PQ fatality and improve long term outcome [8-11]. The outcome obtained for the control group in this study indicated a huge room for further improvement of this method. As reported previously, PQ clearance is apparently more effective with HP [12]. In clinical practice, the causes of mortality from PQ poisoning are multiple organ failure

(acute stage) and lung fibrosis related respiratory failure (sub-acute stage). Although HP can effectively remove PQ from the bloodstream and is widely used for the treatment of PQ intoxication, its efficiency in severe PQ poisoning cases has been disappointing.

Xuebijing (XBJ) is an intravenous preparation made from five traditional Chinese medicines, namely, Chishao (Radix Paeoniae Rubra), Danggui (Radix Angelica Sinensis), Chuanxiong (Rhizoma Chuanxiong), Honghua (Flos Carthami), and Danshen (Radix Salviae Miltiorrhizae). The bioactive roles of XBJ injection include activating circulation, removing blood stasis, and clearing toxins [13]. Indeed, Xuebijing injection has been reported to decrease the blood levels of TNF-α, TGF-β, and IL-6 [14-16] and dramatically improve the SIRS and MODS in the clinic, [17-20] by reducing ultrastructure injury in the lung tissue and preventing pulmonary fibrosis [21, 22]. However, studies assessing the effectiveness of Xuebijing in HP are scarce. Based on our data reported here, it is clear that the combination of Xuebijing injection and HP treatment resulted in improved clinical outcomes (better organ function and reduced lung fibrosis), compared with the control group.

Similarly, ulinastatin also added to the clinical effect of HP on PQ poisoning. PQ is known to be discharged from the kidneys in the form of a prototype, causing renal tubular edema and necrosis, which in turn lead to acute renal failure. The mechanism involves TNF-α induced renal tubular epithelial cell apoptosis. PQ poisoning was shown to induce high expression levels of caspase-3, which plays an important role in the apoptosis pathway [23, 24]. Thus, it was reasonable to assume that ulinastatin protects kidney from the damage by PQ through

inhibiting the release of inflammatory cytokines (such as TNF-α, TGF-β and IL-6), in agreement with our studies.

Conclusions

The lack of a specific antidote for PQ makes improved treatment highly desirable. Based on our studies, the addition of Xuebijing to the standard HP treatment positively impacted prevention of organ damage and protected the lung from progressing to fibrosis; this should be considered anew beneficial approach for current clinical treatments.

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Disclosure of conflict of interest

None.

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References

[1] Yu H, Fang Q. Clinical data analysis of severe acute paraquat poisoning. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi 2010; 28: 786-7.

[2] Dinis-Oliveira RJ, Duarte JA, Sanchez-Navarro A, Remiao F, Bastos ML, Carvalho F. Paraquat poisonings: mechanisms of lung toxicity, clinical features, and treatment. Crit Rev Toxicol 2008; 38: 13-71.

[3] Xu XL, Wang W, Song ZJ, Ding H, Duan XH, Meng HC, Chong J. Imaging in detecting sites of pulmonary fibrosis induced by paraquat. World J Emerg Med 2011; 2: 45-9.

[4] Lin X, Shi S, Dai M. The influence of anisodamine on lung, liver and TNF-α in plasma in rats with paraquat poisoning. Chinese Journal of Practical Medicine 2013; 8: 254-6.

[5] Huan M, Zhang P, Chang X. The dynamic changes of nuclear factor-kB and cytokines on injuried lung in rats with paraquat poisoning. Chinese Journal of Industrial Hygiene and Occupational Diseases 2009; 27: 463-7.

[6] Wang D, Wang L, Pang X. The influence of hemoperfusion combined hemofiltrationon plasma TNF-α, TGF-β in patients with paraquat poi-

soning. Zhongguo Lao Nian Xue Za Zhi 2013; 11: 5545-7.

[7] Liu Y, Qiu Q, Ge Y. Effects of hemoperfusion on plasma concentration and histopathological changes in paraquat poisoning rabbits. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi 2011; 29: 735-9.

[8] Xie Y, Dong C, Du Y. The application of gastrointestinal and blood purification in the treatment of paraquat poisoning. Zhong Guo Gong Ye Yi Xue Za Zhi 2013; 26: 426-9.

[9] Hsu CW, Lin JL, Lin-Tan DT, Chen KH, Yen TH, Wu MS, Lin SC. Early hemoperfusion may improve survival of severely paraquat-poisoned patients. PLoS One 2012; 7: e48397.

[10] Yin K, Zheng X, Xue C. The clinical analysis of different hemoperfusion in patients with acute paraquat poisoning. Zhonghua Quan Ke Yi Xue 2013; 11: 1791-2.

[11] Li Q, Peng X, Yang H, Wang H, Shu Y. Deficiency of multidrug and toxin extrusion 1 enhances renal accumulation of paraquat and deteriorates kidney injury in mice. Mol Pharm 2011; 8: 2476-83.

[12] Kang MS, Gil HW, Yang JO, Lee EY, Hong SY. Comparison between kidney and hemoperfusion for paraquat elimination. J Korean Med Sci 2009; 24 Suppl: S156-60.

[13] Fang K, Wang X. Treatment of multiple organ dysfunction syndrome by Xuebijing injection: a clinical research. Zhongguo Zhong Xi Yi Jie He Za Zhi 2013; 33: 205-7.

[14] S SZ, Zhang W, Li R. The influence on blood hemodynamic effects in rabbit with seawater immersion abdominal injury with the treatment of ulinastatin combined Xuebinjing. Xi Nan Guo Fang Yi Xue 2013; 23: 236-9.

[15] Zheng X, Sun X, Ma P, Liu Z, Jiang N. Therapeutic potential of intravenous Xuebijing on transforming growth factor beta1 and procollagen type III peptide in patients with acute paraquat poisoning. J Tradit Chin Med 2012; 32: 584-9.

[16] Liu YK, Huang LJ, Zhao S, Lin W, He JB, Ying L, You X, Wang WT. [Effect of Xuebijing injection on TLR4--NF-Kappa B--IL-1 beta pathway of myocardial hypoxia/reoxygenation in rats]. Zhongguo Ying Yong Sheng Li Xue Za Zhi 2014; 30: 55-9.

[17] Yin Q, Li C. Treatment effects of xuebijing injection in severe septic patients with disseminated intravascular coagulation. Evid Based Complement Alternat Med 2014; 2014: 949254.

[18] Chen Y, Li C. Randomized controlled multicenter study for the treatment of sepsis with Xuebijing. Zhonghua Ji Zhen Yi Xue Za Zhi 2013; 22: 130-5.

[19] Ji J, Zhou F, Yue H, Song Q. Protective mechanism of Xuebijing injection against heat stroke in rats. Exp Ther Med 2014; 7: 1745-51.

[20] Yao X, Zhag Y, Sun C. Protective effects of Xuebijing effervescent table on vital organs in rats with toxic injury induced by endotoxin. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue 2012; 24: 357-9.

[21] Hu M, Wu W, Gong J. The interventional effect of Xuebijing injection on expression of mitochondrial fusion protein 2 and ultrastructure change in lung tissues in rats with paraquat poisoning. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2014; 26: 388-93.

[22] Wang L, Xu Q, Huang S. Effects of methylprednisolone plus Xuebijing on bleomycin-induced acute exacerbation of pulmonary fibosis in rats. Zhonghua Yi Xue Za Zhi 2014; 94: 301-5.

[23] Liu J, Liu J, Mao J, Yuan X, Lin Z, Li Y. Caspase-3-mediated cyclic stretch-induced myoblast apoptosis via a Fas/FasL-independent signaling pathway during myogenesis. J Cell Biochem 2009; 107: 834-44.

[24] Li J, Han B, Ma X, Qi S. The effects of propofol on hippocampal caspase-3 and Bcl-2 expression following forebrain ischemia-reperfusion in rats. Brain Res 2010; 1356: 11-23.