Original Article
Effects of continuous blood perfusion on myocardial enzyme indexes and sleep quality in elderly patients with severe organophosphorus pesticide poisoning

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Abstract: Objective: To explore the effect of continuous blood perfusion on myocardial enzyme indexes and sleep quality in elderly patients with severe organophosphorus pesticide poisoning. Methods: A total of 82 elderly patients with severe organophosphorus pesticide poisoning were divided into an observation group and a control group, 41 cases each. On the basis of conventional emergency treatment for both groups of patients after admission, the control group was given a single blood perfusion treatment. And the observation group was given continuous blood perfusion therapy which means two perfusions with a duration of 120-150 min/time were performed within 12 hours after admission. If the patient's M symptoms or nicotine-like symptoms persist after 2 blood perfusions and acetylcholinesterase (AChE) activity is <50%, a third session was performed. The clinical parameters, myocardial enzyme spectrum indexes, sleep quality, changes in inflammatory factors and incidence of complications were compared between the two groups. Results: Compared with the control group, the duration of coma, M symptoms, central nervous system symptoms and hospitalization time of the observation group were shortened, and the recovery time of AChE activity was advanced (all P<0.001). During the treatment, there were 3 deaths in the control group and 1 death in the observation group. After we excluded the deaths, the levels of creatine kinase, creatine kinase isoenzyme, lactate dehydrogenase, α-hydroxybutyrate dehydrogenase and C-reactive protein, interleukin-6 and tumor necrosis factor-α in the two groups were found to be lower than those before treatment, and the levels in the observation group was lower than those in the control group (all P<0.001). After treatment, the Pittsburgh Sleep Quality Index score of the observation group was significantly lower than that of the control group (P<0.001). The incidence of complications in the observation group was lower than that in the control group (P<0.05). Conclusion: The combination of continuous blood perfusion on the basis of conventional treatment could improve the inflammatory state of the organism in elderly patients with severe organophosphorus pesticide poisoning. It restored AChE activity shortly, relieved symptoms of toxicity, reduced the degree of myocardial damage, improved sleep quality, and have high safety.

Keywords: Continuous blood perfusion, severe organophosphorus pesticide poisoning, myocardial enzymes, sleep quality, inflammatory factors

Introduction

There are many types of organophosphorus pesticides. After poisoning, the disease progresses rapidly and the lethal rate is high [1]. After organophosphorus pesticide poisoning, the patient's acetylcholinesterase (AChE) activity is inhibited, and parasympathetic nerve excitability is enhanced, which manifests as M action, such as increased secretion of respiratory tract glands, hypoxia, dyspnea, etc., which

in severe cases can cause respiratory failure and eventually lead to death [2, 3]. For severe organophosphorus pesticide poisoning, resuscitation such as gastric lavage and diarrhea catheterization should be performed as soon as possible, and treatment such as atropine and pralidoxime iodide should be given at an early time [4]. Blood perfusion is a kind of blood purification technology, which is a common and effective rescue solution for the treatment of severe organophosphorus pestici-

Table 1. Comparison of baseline data (n, $\bar{x} \pm sd$)

Indexes	Observation group (n=41)	Control group (n=41)	χ^2/t	P
Gender (n)			0.198	0.656
Male	19	17		
Female	22	24		
Age (year)	66.60±4.50	67.90±5.30	1.197	0.235
BMI (kg/m^2)	22.20±3.20	22.64±2.77	0.666	0.508
Organophosphorus pesticide types (n)			0.274	0.470
Dichlorvos	14	12		
Paraquat	9	11		
Methamidophos	7	8		
Trichlorfon	4	3		
Phoxim	4	3		
Other	3	4		
Interval between poisoning and admission (h)	4.53±2.10	4.37±1.74	0.376	0.708

Note: BMI: body mass index.

de poisoning [5]. Blood perfusion is to remove the inflammatory mediators and toxic substances present in the circulatory system through the principle of adsorption. It can improve the damage of organophosphorus pesticides to the body and achieve therapeutic effects [6]. Organophosphorus pesticides are mainly absorbed into the human body through the respiratory tract, skin and mucous membranes, and then rapidly distributed in the tissues and organs of the body with the blood circulation. It is highly toxic to the liver, heart and so on [7]. A study of Costa has shown that patients can suffer varying degrees of myocardial damage following organophosphate pesticide poisoning, noting that myocardial damage is one of the direct factors leading to death of patients and whether myocardial damage can be improved by blood purification in patients with organophosphorus pesticide poisoning has become a heated topic of research [8]. The purpose of this study was to investigate the effects of continuous blood perfusion on myocardial enzymes, inflammatory factors, and sleep quality in elderly patients with severe organophosphorus pesticide poisoning, and to analyze their safety.

Materials and methods

General information

Eighty-two elderly patients with severe organophosphorus pesticide poisoning who were treated in Affiliated Renhe Hospital of China Three Gorges University from February 2017 to January 2020 were divided into two groups according to random number table. The observation group and the control group were each 41 cases and the general information of two groups was shown in **Table 1**. Inclusion criteria were listed as follows: patients whose age >60 years; patients with oral administration and single pesticide poisoning; patients with severe organophosphorus pesticide poisoning, which refers to patients with the clinical manifestations of important organ failures such as pulmonary edema, cerebral edema, and respiratory failure in addition to muscarinic and nicotinic symptoms; patients whose AChE activity was less than 30% of normal value; delirious or unconscious patients whose informed consent was signed by the patient's family. Exclusion criteria were listed below: patients who have heart failure and cannot be easily treated with blood perfusion therapy; patients with mild or moderate organophosphorus pesticide poisoning; patients with malignant tumors. Patients who died during treatment or lost their appointments were excluded. This study was approved by the medical Ethics Committee of Affiliated Renhe Hospital of China Three Gorges University.

Methods

After admission, both groups of patients were given conventional emergency treatment immediately, including gastric lavage and catharsis. Intravenous atropine sulfate injection

(Chengdu First Pharmaceutical Co., Ltd., specification: 2 mL:1 mg, country of origin: China) was also given at an initial dose of 0.5-2.0 mg to ensure atropine within 1-2 h and then the injection was reduced or maintained at an interval of 1-2 h according to the patient's specific condition. Intravenous chlorpyrifosine injection (China Resources Shuanghe Pharmaceutical Co., Ltd., specification: 2 mL:0.5 g, country of origin: China) of 1.5-2.0 g was administrated and repeated administration of the drug was determined by patient's condition until the symptoms of toxicity disappeared and the AChE activity was above 50%-60%.

The control group was given a single blood perfusion treatment, which meant that vascular access was established on the basis of heparin anticoagulation after admission, and then the perfusion machine (Beijing Zhongxi Yuanda Technology Co., Ltd., model: M150JF-800A, country of origin: China) was set up with a flow rate of 100-200 mL/min and a perfusion time of 120-150 min for perfusion treatment. The observation group was given continuous blood perfusion treatment and the number of perfusion was determined by patient's actual condition with generally 2 to 3 times. Two blood perfusions were performed within 12 hours after admission, and the perfusion time was 120 to 150 min/time. The third blood perfusion was performed if patient's M symptoms or nicotinic manifestations were still present and AChE activity <50% after perfusion for twice. During the treatment, the patient's vital signs were closely monitored, and patients with severe complications immediately stopped perfusion therapy.

Outcome measures

Main outcome measures: (1) The clinical indicators of the two groups of patients were compared, the duration of coma, the recovery time of AChE activity, the duration of poisoning symptoms (M symptoms and central nervous system symptoms) and the length of hospitalization were recorded. (2) A sample of 5 mL of venous blood was drawn from every patient in two groups before and after treatment (the time point after treatment was based on the blood perfusion of the observation group and the blood samples of the two groups were collected at the same time), centrifuged at 3,000 rpm for 10 min after coagulation, and then the serum was taken for use. The levels of creatine kinase (CK), creatine kinase isoenzyme (CK-MB), lactate dehydrogenase (LDH), and α-hydroxybutyrate dehydrogenase (α-HBDE) were measured using an automatic biochemical analyzer (Beckman Coulter, USA, model: LH 750, country of origin: USA). (3) The Pittsburgh Sleep Quality Index (PSQI) was used to evaluate the sleep quality of the two groups of patients after treatment (with the patient waking up and falling back to sleep as the time point of detection) [9]. The PSQI consists of 6 aspects of sleep duration, sleep disturbance, sleep quality, daytime dysfunction, sleep efficiency and hypnotic medication, with a total of 18 points. The lower the score, the better the sleep quality.

Secondary outcome measures: (1) The above-mentioned spare serum was taken and used for enzyme-linked immunosorbent assay (ELISA) to detect serum C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) levels. The kits were purchased from Shanghai Enzyme Biotechnology Co., Ltd. The product codes were ml220482, ml058097, ml077385, and the origin was China. (2) Statistics on the occurrence of complications during hospitalization of two groups of patients, such as pulmonary fibrosis, stress ulcers, multiple organ failure, etc.

Statistical analysis

SPSS 20.0 was used for data analysis. The count data was expressed as a percentage (%). Except for the fisher's exact probability method for the comparison of individual complications, the comparison of other count data was tested by χ^2 test. The measurement data was expressed as mean ± standard deviation ($\bar{x}$ ± sd). The paired t test was used for comparison between before and after treatment in the same group, and the independent t test was used for comparison between the two groups. $P < 0.05$ was considered statistically significant.

Results

Baseline information

The data of two groups on gender, age, body mass index, organophosphorus pesticide type and interval between poisoning and admission

Table 2. Comparison of clinical indicators ($\overline{x} \pm sd$)

Group	Observation group (n=40)	Control group (n=38)	t	P
Duration of coma (h)	9.64±2.10	12.48±3.27	4.537	<0.001
Recovery time of ache activity (d)	6.50±1.45	8.97±2.30	5.640	<0.001
Duration of M symptoms (d)	1.90±0.46	2.88±0.57	8.330	<0.001
Duration of central nervous system symptoms (d)	7.79±2.20	11.98±2.77	7.373	<0.001
Length of hospitalization (d)	10.85±2.28	15.57±3.50	7.017	<0.001

Table 3. Comparison of myocardial enzyme spectrum index levels between two groups of patients before and after treatment ($\overline{x} \pm sd$)

Indexes	Before or after treatment	Observation group (n=40)	Control group (n=38)	t	P
CK (U/L)	before	1567.79±203.48	1593.04±214.50	0.533	0.596
	after	454.57±45.50***	876.80±65.79***	32.801	<0.001
CK-MB (U/L)	before	61.10±9.66	61.75±9.20	0.304	0.762
	after	32.29±7.84***	40.40±8.65***	4.331	<0.001
LDH (U/L)	before	404.49±76.60	410.75±80.27	0.352	0.726
	after	246.08±64.74***	334.48±76.40***	5.499	<0.001
α-HBDE (U/L)	before	377.79±40.04	384.40±45.67	0.678	0.450
	after	188.85±32.17***	295.48±37.74***	13.396	<0.001

Note: Compared with the same group before treatment, ***P<0.001. CK: creatine kinase; CK-MB: creatine kinase isoenzyme; LDH: lactate dehydrogenase; α-HBDE: α-hydroxybutyrate dehydrogenase.
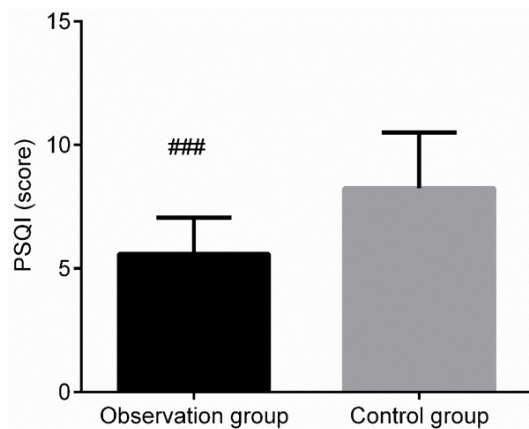
Figure 1. Comparison of sleep quality after treatment. Compared with the control group, ###P<0.001. PSQI: Pittsburgh Sleep Quality Index.

were compared. None of the differences were statistically significant (P>0.05), and the groups were comparable, as shown in **Table 1**.

Clinical indicators

During treatment, there were 3 deaths in the control group and 1 death in the observation group. Compared with the control group, the duration of coma, M symptoms, central nervous system symptoms and hospitalization time of the observation group were shortened. The recovery time of AChE activity was advanced (all P<0.001), as shown in **Table 2**.

Myocardial enzyme spectrum

After the death cases were excluded, the levels of CK, CK-MB, LDH and α-HBDE after treatment in the two groups were lower than those before treatment, and those levels of the observation group was lower than those of the control group (all P<0.001), as shown in **Table 3**.

Sleep quality

After the death cases were excluded, the point when patient fell asleep again after being awake was taken as the detection time point, and the PSQI score of the patient was evaluated. The PSQI scores of the observation group and the control group were (5.59±1.47) and (8.25±2.26) points, respectively. The PSQI score of the observation group after treatment was significantly lower than that of the control group (P<0.001), as shown in **Figure 1**.

Table 4. Comparison of inflammatory factor levels between two groups of patients before and after treatment ($\bar{x} \pm sd$)

Indexes	Before or after treatment	Observation group (n=40)	Control group (n=38)	t	P
CRP (mg/L)	before	56.69±5.40	57.10±6.23	0.310	0.757
	after	20.02±4.29***	28.87±5.10***	8.272	<0.001
IL-6 (pg/mL)	before	80.80±10.81	81.75±11.48	0.376	0.708
	after	39.40±5.40***	52.10±6.64***	9.239	<0.001
TNF-α (ng/L)	before	73.30±7.75	74.15±6.80	0.516	0.608
	after	37.58±6.40***	45.70±5.52***	6.010	<0.001

Note: Compared with the same group before treatment, ***$P<0.001$. CRP: C-reactive protein; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α.

Table 5. Occurrence of complications in two groups (n, %)

Groups	Pulmonary fibrosis	Stress ulcers	Multiple organ failure	Occurrence
Observation group (n=41)	1 (2.44)	1 (2.44)	1 (2.44)	3 (7.32)
Control group (n=41)	3 (7.32)	6 (14.63)	3 (7.32)	12 (29.27)
χ^2	0.263	2.499	0.263	6.609
P	0.608	0.114	0.608	0.010

Inflammatory factors

After the death cases were excluded, the levels of CRP, IL-6, and TNF-α in the two groups decreased after treatment, and those levels of the observation group was lower than those of the control group (all P<0.001), as shown in **Table 4**.

Complications

During treatment, the complication rate of the observation group was 7.32%, which was significantly lower than that of the control group (29.27%, P<0.05), as shown in **Table 5**.

Discussion

The salvage purpose of organophosphorus pesticide poisoning is to remove poisons, restore AChE activity, and reduce mortality. Atropine combined with cholinesterase recuperative drugs is a commonly used treatment in clinic. Atropine can effectively relieve M symptoms, but it cannot reactivate inactivated AchE [10, 11]. Cholinesterase rejuvenating drugs can promote the revitalization of inhibited or inactivated AChE and improve patients' nicotine-like toxic effects, but neither of them can clear the poison that enters the body's blood circulation, so the therapeutic effect is limited [12].

Blood perfusion is to drain the patient's blood into the perfusion device and use the adsorption of carbon activated and macroporous polymer resin to remove poisons and metabolites with strong fat solubility, large molecules or high binding rate with lipoproteins. This can achieve the purpose of blood purification, which is often used clinically to rescue poisoning such as organophosphorus pesticides and barbiturates [13, 14]. Blood perfusion for once is usually not sufficient to completely remove organophosphorus toxins from the body of a patient with severe organophosphorus pesticide poisoning, and blood perfusions for 2-3 times are usually required. Combined blood perfusion with conventional treatment to treat organophosphorus pesticide poisoning patients, Liu et al. found that the duration of symptoms and hospitalization were significantly shortened and the mortality rate was reduced [15]. Reeves et al. found that patients with maintenance hemodialysis have significantly improved their sleep disturbances after receiving hemodialysis treatment, which is considered to be related to the removal of macromolecular metabolic poisons by the blood perfusion [16]. Similar results were found in this study. The duration of coma, M symptoms, central nervous system symptoms and the length of hospitalization in the observation group were shortened, the recovery time of AChE

activity was advanced, and the PSQI score and incidence of complications were also significantly lower than those in the control group. This suggested that the combination of continuous blood perfusion on the basis of conventional treatment was more effective for the treatment of elderly patients with severe organophosphorus pesticide poisoning. It can restore AChE activity very fast, relieve the symptoms of poisoning, improve their sleep quality, and have high safety without serious complications.

Organophosphorus pesticide poisoning can cause myocardial damage and result in serious complications such as respiratory, circulatory failure, toxic myocarditis and even cardiac arrest. It appears as a change in myocardial enzyme spectrum and electrocardiogram in the auxiliary examination, which is the main lethal factor [17, 18]. The monitoring of serum myocardial enzyme spectrum can directly reflect the degree of myocardial injury. Tomizawa et al. studied the effect of blood perfusion on myocardial enzyme levels in patients with organophosphorus pesticide poisoning, and found that the four levels of myocardial enzymes decreased after treatment, so it was concluded that blood perfusion can reduce the degree of myocardial damage in patients with organophosphorus pesticide poisoning [19]. This study also has similar research results. After excluding death cases, the levels of CK, CK-MB, LDH and α-HBDE in the two groups after treatment were lower than before treatment, and the levels of myocardial enzymes in the observation group were significantly lower than those in the control group. This suggested that the combination of continuous blood perfusion on the basis of conventional treatment could significantly reduce the degree of myocardial damage in elderly patients with severe organophosphorus pesticide poisoning. It is speculated that the blood purification effect of blood perfusion not only removes poisons but also removes harmful substances to the heart muscle. After organophosphorus pesticides enter the body, they can activate the immune system to release a number of inflammatory mediators. Yang et al. found that the levels of inflammatory factors such as CRP and IL-6 in patients with severe organophosphorus pesticide poisoning showed a pathological increase, and believed that abnormally increased inflammatory mediators are the main cause of multiple organ dysfunction [20]. A number of inflammatory mediators

released can prevent the disease from worsening and reduce the risk of death. Shaffo et al. have shown that timely and effective removal of inflammatory mediators is beneficial to improve the prognosis and outcome of patients with organophosphorus pesticide poisoning, and believes that the recovery of AChE activity is also related to the removal of inflammatory mediators [21]. Early continuous blood perfusion can effectively remove CRP, IL-6 and other inflammatory factors in the blood circulation, control the body's inflammation progress, and have a positive effect on the therapeutic effect [22, 23]. In this study, after excluding death cases, the serum CRP, IL-6, and TNF-α levels of the observation group after treatment were lower than those of the control group, suggesting that combined with continuous blood perfusion on the basis of conventional treatment can significantly improve the inflammatory state of elderly patients with severe organophosphorus pesticide poisoning. However, this study had a small sample size and it did not explore the specific mechanism by which continuous blood perfusion contributed to this finding, which is a direction of future research.

In summary, combined with continuous blood perfusion on the basis of conventional treatment can improve the inflammatory state of the elderly patients with severe organophosphorus pesticide poisoning, restore AChE activity at an early time point, relieve the symptoms of poisoning, alleviate the degree of myocardial damage, improve sleep quality, and have high safety.

Disclosure of conflict of interest

None.

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