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Clinical study and observation on the effect of hemoperfusion therapy treatment on central nervous system injury in patients with 2,4-dichlorophenoxyacetic acid poisoning

J. LIU, R.-X. LI, C.-S. YANG, L.-L. ZHAO, X. LIU, B. ZHANG

Department of Emergency Medicine, Qinghai Provincial People's Hospital, Xining, China

Abstract. – OBJECTIVE: To evaluate the curative effect of hemoperfusion therapy on central nervous system injury in patients with 2,4-dichlorophenoxyacetic acid poisoning.

PATIENTS AND METHODS: A total of 60 patients with 2,4-dichlorophenoxyacetic acid poisoning were enrolled in this study. They were admitted to the Emergency Department of Qinghai Provincial People's Hospital from 2015 to 2018 and were randomly divided into two groups by random number table method. One group was control group (routine treatment group), and the other group was the treatment group (hemoperfusion therapy was added on the basis of routine treatment). Glasgow coma score (GCS), APACHE II score, and MMSE score were used to evaluate the effects before treatment and 7 days after treatment. The results were statistically analyzed.

RESULTS: After treatment, GCS in the treatment group was higher than that in the control group, while APACHE II score was lower than that in the control group, and MMSE score was significantly higher than that in the control group, with statistically significant difference ($p<0.05$). The effective rate in the control group was only 26.67%, and that in the treatment group was 86.67%, with statistically significant difference ($\chi^2=19.62$, $p<0.001$).

CONCLUSIONS: Hemoperfusion therapy can promote the recovery of central nervous system in patients with 2,4-dichlorophenoxyacetic acid poisoning, reduce the injury of other organs, and significantly reduce the mortality of patients.

Key Words:
Hemoperfusion therapy, 2,4-dichlorophenoxyacetic acid, Central nerve system, Injury, Curative effect, Clinical study.

Introduction

2,4-dichlorophenoxyacetic acid is also known as 2,4-D butyl ester, 2,4-dichlorophenoxyacetate butyl ester and butyl 2,4-dichlorophenoxyacetate[1]. It is a kind of phenoxyalkanoic acids herbicide widely used in Qinghai province, China at present. It is a unique herbicide poisoning in this region, and the acute poisoning death rate is high. Ingestion, skin contact and inhalation are three main routes of human exposure to 2,4-D herbicides. Metabolic acidosis, hyperventilation, hyperkalemia, hyperthermia, elevated creatine kinase, systemic muscle stiffness, hypotension or arrest were the criteria for severe toxicity[2]. Various mechanisms of toxicity include dose-dependent membrane damage, oxidative phosphate coupling and acetyl CoA metabolism disruption[2]. Coma or coma may be caused by direct central nervous system inhibition or metabolic disorder. During systemic toxicity, hyperreflexia, ataxia, nystagmus, mydriasis, hallucination, convulsion, fasciculation and paralysis may occur at different intervals[3]. These endotoxins are typical pathogen-associated molecules present in patients with 2,4-D herbicide poisoning. From 1986 to 2004, totally 852 cases of 2,4-dichlorophenoxyacetic acid poisoning were treated in our hospital. Among these patients, 845 died, with a mortality rate of 99.17%. It has attracted close attention both domestic and overseas. However, there is no specific antidote to this compound so far. Since the initial manifestations are not very different from anticholinesterase poisoning, the chances of misdiagnosis are high[4]. 2,4-dichlorophenoxyacetic acid stimulates cholinergic nervous system in the body[5], reduces insulin secretion, inhibits synthesis of adrenocortical hormone. It mainly damages central nervous system, and is also harmful to liver, heart, kidney, lung and stimulates gastrointestinal tract, finally leads to death. The central nervous system suffers the most damage. Therefore, it is vital and urgent to study the effective treatment of 2,4-dichlorophenoxyacetic acid. Due to the characteristics of the regional use of this

Corresponding Author: Bin Zhang, MD; e-mail: znlj9463@163.com

herbicide, there are few reports on the herbicide, but only case reports[6,7]. The treatment of 2,4-dichlorophenoxyacetic acid poisoning is still at the exploratory stage, and there is no satisfactory treatment plan. Hemoperfusion is an extracorporeal treatment based on adsorption, historically reserved for the treatment of acute poisonings. It was even preferred over hemodialysis in the management of overdosed patients[8]. Hemoperfusion is suitable for non-dialysis drugs, and it has a better effect than hemodialysis for poisons with large molecular weight, water-insoluble, and protein-bound. Sixty patients with 2,4-dichlorophenoxyacetic acid poisoning were admitted to our hospital. They were divided into two groups, one group received hemoperfusion (hemoperfusion therapy) plus routine treatment, the other group received routine treatment. The central nervous system injury degree and recovery before and after treatment were evaluated by Glasgow coma score (GCS), APACHE II score, and MMSE score. The effect of hemoperfusion treatment on central nervous system injury in patients with 2,4-dichlorophenoxyacetic acid poisoning was analyzed.

Patients and Methods

Patients

Sixty patients with 2,4-dichlorophenoxyacetic acid poisoning were enrolled in this study. They were admitted to Qinghai Provincial People's Hospital from 2015 to 2018. The patients were randomly divided into two groups: hemoperfusion therapy group (treatment group) and routine treatment group (control group), with 30 cases in each group. Patients and their families were informed and signed informed consent forms. The general data of the patients were counted, including age, gender, doses and time from taking the medicine to admission, GCS, APACHE II score, MMSE score and various biochemical examination results, including whole blood cell analysis and blood gas analysis, functions of liver, kidney, heart, and other organs, and six items of coagulation. This study was approved by the Ethics Committee of our hospital.

Therapies

Control group: patients were given routine water gastric lavage, catharsis, fluid replacement, sedation, acid suppression, dehydration, diuresis and decorporation, support symptomatic treatment, etc. Treatment group: on the basis of routine treatment, hemoperfusion (HA230 hemoperfusion device q12h manufactured by Zhuhai Jianfan Biotechnology Co., Ltd.) was given for two hours each time for three consecutive days.

Evaluation Methods Before and After Treatment

All patients were evaluated with scale before treatment and 7 days after treatment. (1) GCS was used for assessment, with a total score of 15 points and a minimum of 3 points. According to the score, the degree of consciousness disorder was assessed. 13-14 points were classified as mild disorders, 9-12 as moderate disorders, and 3-8 as severe disorders (mostly coma). (2) APACHE II score was used for assessment. The higher the score was, the more critical the condition was. (3) Mini-mental state examination (MMSE) was adopted. The scale includes 7 aspects: time orientation, location orientation, immediate memory, attention and calculation, delayed memory, language and visual space. Score 27-30 was normal, score < 27 was cognitive impairment, score 21-26 was mild, score 10-20 was moderate, and score 0-9 was severe.

Curative Effect Evaluation

After the treatment, the curative effect was evaluated and classified as "improved" and "ineffective". "Improved": the function of each organ of the patient was improved, and the degree of consciousness disorder was reduced. "Ineffective": there was no evident improvement of symptoms and signs or death of the patient. Effective rate (%) = improved / total cases × 100%.

Statistical Analysis

All data were analyzed by SPSS 19.0 (IBM, Armonk, NY, USA) The measurement data of normal distribution were expressed by $\bar{\chi}\pm S$, *t*-test was adopted for comparison between groups. Enumeration data were expressed by frequency and rate, and χ^2-test or Fisher' s precise test adopted. $p<0.05$ was considered statistically significant.

Results

Comparison of General Data

The control group consisted of 30 people, including 14 males and 16 females, with an average age of 35.93±15.87 years old. The time between admission and medication was 12.80±16.74 hours, the maximum age was 69 years old, the minimum

age was 14 years old. The dosage was 85.00±73.19 ml, the maximum dosage was 300 ml, and the minimum was 20 ml. The patient's body temperature at admission was 36.73±0.83°C, and the maximum body temperature was 38°C. The admission heart rate was 90.73±17.65 beats/min, the admission respiratory rate was 18.50±3.30 beats/min, and the admission blood pressure was 110.80±17.3/68.23±10.70 mmHg. There were 30 people in the hemoperfusion therapy group, including 15 men and 15 women, with an average age of 36.10±15.76 years old. The time between admission and medication was 13.00±13.08 hours, the maximum age was 71 years old, the minimum age was only 16 years old. The dosage was 85.33±71.76 ml, the maximum dosage was 350 ml, and the minimum was 40 ml. The patient's body temperature at admission was 36.73±0.91°C, and the maximum body temperature was 39°C. The admission heart rate was 90.77±17.66 beats/min, the admission respiratory rate was 18.57±2.97 beats/min, and the admission blood pressure was 111.03±17.26/68.10±10.37 mmHg. There was no statistical difference (t_{age} =0.96, p=0.34; $t_{medication\ time}$ =0.15, p=0.88; t_{dosage} =0.14, p=0.89; $t_{admission\ temperature}$ =0.16, p=0.85; $t_{admission\ heart\ rate}$ =0.19, p=0.84; $t_{admission\ respiratory\ frequency}$ =0.34, p=0.74; $t_{blood\ pressure}$ =0.42, p=0.67).

Comparison of Scores of Observation Indexes Before and After Treatment Between the Two Groups

There was no statistical difference in GCS, MMSE score and APACHE II score between the two groups before treatment ($p > 0.05$). After 7 days of treatment, the GCS and MMSE score of the treatment group were significantly higher than those of the control group (routine treatment group), and the APACHE II score of the treatment group was significantly lower than that of the control group ($p<0.05$). The GCS, APACHE II, and MMSE scores before and after treatment were also significantly different between the two groups ($p<0.01$). The difference between the two groups before and after treatment was statistically significant, indicating that for patients with 2,4-dichlorophenoxyacetic acid poisoning, ordinary treatment had certain effects on mild and moderate patients, but the mortality rate of patients with severe poisoning was still extremely high. If conditions permitted, hemoperfusion therapy was an efficient treatment method for patients with moderate and severe poisoning, which can greatly reduce the mortality rate, improve the symptoms of organ damage and nervous system damage of patients and shorten the hospitalization time of patients. It is worthy of wide clinical recommendation (Tables I and II).

Comparison of Clinical Curative Effect

There were 22 patients died in the control group. Among them, 17 patients died in hospital, 5 patients died after automatic discharge, and the remaining 8 patients were discharged after clinical improvement. There were 4 patients died in the treatment group after discharge. The other 26 patients in the treatment group discharged with clinical standard improvement. One patient in the control group had mild subarachnoid hemorrhage when admitted to hospital. After conservative treatment, the hemorrhage was significantly absorbed when discharged from hospital. According to the above calculation method, the effective rate of the control group was only 26.67%, and that of the treatment group was 86.67%. The difference between the two groups was statistically significant (χ^2=19.62, $p<0.001$). As shown in Table III.

Table I. Comparison of GCS and APACHE II score results between the two group before and after treatment.

Score	Time	Control group (n=30)	Treatment group (n=30)	*t*-value	*p*-value
APACHE II score	Before treatment	14.80-2.22	14.90-1.85	0.68	0.50
	After treatment	12.10-2.59	5.47-2.78	10.33	<0.001
t-value		5.44	16.77		
p-value		<0.001	<0.001		
GCS	Before treatment	4.93-1.51	5.03-1.47	0.26	0.80
	After treatment	6.93-4.75	11.60-3.39	4.38	<0.001
t-value		2.20	10.77		
p-value		0.036	<0.001		

Table II. Comparison of MMSE score results between the two groups after treatment.

Rating scale	Normal	Moderate cognitive impairment	Severe cognitive impairment
Control group (n=30)	11	7	12
Treatment group (n=30)	26	2	2
χ^2		16.00	
p-value		<0.001	

Discussion

At present, there are few studies on 2,4-dichlorophenoxyacetic acid. Ingestion, skin contact and inhalation are three main routes of human exposure to 2,4-D herbicides[9]. Management is only supportive with alkaline diuresis and treatment of complications[10]. This poison does not have any specific antidote, we found a role of forced alkaline diuresis searched the literature on this poison and in its management. Hemoperfusion is suitable for ingesting a large number of toxicants, which has reached the lethal dose, and the clinical symptoms are severe. The general treatment effect is expected to be poor, accompanied by liver and kidney damage and severe complications. Various humoral mediators, including inflammatory cytokines, have been demonstrated to be involved in the pathogenesis of septic shock and sepsis-associated organ dysfunction. As an extracorporeal blood purification technique, hemoperfusion therapy has been only used in the treatment of acute poisoning for many years. We used hemoperfusion therapy to treat central nervous system injury caused by 2,4-dichlorophenoxyacetic acid poisoning. At present, our study reported the largest number of cases, and a control study was carried out to evaluate the curative effect of hemoperfusion therapy on central nervous system injury in patients with 2,4-dichlorophenoxyacetic acid poisoning, providing data support for standardized treatment of 2,4-dichlorophenoxyacetic acid poisoning in the future, which is of great significance. We analyzed the difference in clinical effective rate and mortality between the treatment group and the control group. The effective rate of the control group was only 26.67%, while that of the treatment group was 86.67%, with statistically significant difference (χ^2=19.62, p <0.001), suggesting that hemoperfusion therapy cn significantly benefit patients with 2,4-dichlorophenoxyacetic acid poisoning, which is worthy of strong recommendation in clinic. Hemoperfusion therapy can promote the recovery of central nervous system in patients with 2,4-dichlorophenoxyacetic acid poisoning. According to the analysis of GCS, APACHE II score and MMSA score before and after treatment, GCS and MMSE score of the treatment group were significantly higher than those of the control group, while the APACHE II score of the hemoperfusion therapy treatment group was significantly lower than that of the control group (p<0.05). In clinical treatment of patients with 2,4-dichlorophenoxyacetic acid poisoning, hemoperfusion therapy treatment should be actively recommended. This treatment could reduce the central nerve damage of patients, promote the recovery of the patient's nervous system, improve the damage of other organs, and accelerate the recovery of patients. 2,4-dichlorophenoxyacetic acid is a chlorophenoxy compound[11], which is insoluble in water, soluble in various organic solvents, highly volatile and decomposes with alkali. The exact mechanism of phenoxy herbicides toxicity is unclear. Acute lethal levels of 2,4-D in the plasma appear to lie between 447 mg/liter and 826 mg/liter. Its toxic effects involve heart, central and peripheral nervous systems, liver, kidneys, muscles, lungs and endocrine

Table III. Analysis of clinical curative effect of the two groups.

Group	No. of cases	Clinical curative effect		Total effective rate (%)	χ^2	*p*-value
		Improved	Ineffective			
Control group (n=30)	30	8	22	26.67	19.62	<0.001Δ
Treatment group (n=30)	30	26	4	86.67		

Note: Δ correction for continuity of fourfold table.

system[12] and there is no specific antidote for 2,4-D herbicide poisoning[13]. The LD50 of oral exposure in rats is 150-500 mg/kg. In animal experiments, 2,4-dichlorophenoxyacetic acid can cause demyelination of peripheral nerves, inhibit ribonuclease synthesis, arrest oxidative phosphorylation of cells, and increase liver peroxidase. However, the damage to the central nervous system is still unclear at present. Through the analysis of our research results, we inferred that 2,4-dichlorophenoxyacetic acid can still enter central nervous system through the blood-brain barrier.

Mild and moderate acute poisoning symptoms of 2,4-dichlorophenoxyacetic acid are generally mild, mainly caused by skin contact or respiratory tract exposure. Severe acute poisoning patients have severe symptoms and often lead to death, mainly through intentional poisoning. The main symptoms include mucous ulceration, miosis, coma, high fever, hypotension, vomiting, tachycardia, bradycardia, muscle rigidity, rhabdomyolysis, renal failure, acute lung injury and respiratory failure. Death is often secondary to cardiac arrest, which is common in clinic. There are also related reports[14] showing late-onset hyperthermia, electrolyte disturbance such as hypocalcemia, hyperkalemia and hypophosphatemia, thrombocytopenia or leukopenia. Some patients even have hyperglycemia or allergic symptoms. Chronic poisoning patients suffer from neurotoxicity, such as hypomnesia. There are also reports of reproductive toxicity. It may even lead to soft tissue sarcoma and non-Hodgkin lymphoma[15]. Pre-hospital treatment for 2,4-dichlorophenoxyacetic acid poisoning includes removing toxic clothes, exposing skin, scrubbing with alkaline soapy water, and washing with large amount of alkaline water if eyes are in contact. In the treatment after admission, activated carbon adsorption is used. Diazepam can be considered in case of central nervous system abnormality, epileptic seizure and convulsion. Breathing and ECG should be closely monitored. Alkaline diuresis and intravenous injection of sodium bicarbonate 1-2 mg/kg should be given. Other measures include large amount of fluid replacement, continuous intravenous drip of sugar saline, close monitoring of blood gas and adjustment of pH of urine. In hemoperfusion therapy, the patient's blood is led out of the body through a purification device to remove pathogenic substances and purify the blood. Hemoperfusion therapy includes hemodialysis, hemofiltration, hemoperfusion, plasma exchange, immunoadsorption, etc. It has been reported in a literature[13] that hemodialysis may have poor efficacy. The pathogenic substances cannot be quickly and efficiently removed due to the high binding rate of 2,4-dichlorophenoxyacetic acid protein (60-80%). However, hemoperfusion may be effective. Currently, there are few studies and no relevant literature references. We found through this study that hemoperfusion therapy has an exactly accurate curative effect on 2,4-dichlorophenoxyacetic acid central nervous toxicity. There are few studies on pharmacokinetics of 2,4-dichlorophenoxyacetic acid in human body. One study[4] suggests that the half-life of its oral administration is 10-20 hours, that of intravenous injection is about 12 hours, and that of skin and mucosa contact is about 40 hours. If urine is alkalized, the half-life will be significantly shortened. The World Health Organization has reported[1] that the minimum toxic dose (oral) of 2,4-dichlorophenoxyacetic acid is 40-50 mg/kg, and the lethal dose (oral) is 80 mg/kg. If injected intravenously, the lowest toxic dose is 28 mg/kg, and the lethal dose is 50 mg/kg. At present, there are no related research and reports in China. Hemoperfusion therapy is the most commonly used clinical blood purification technique to treat acute poisoning. At present, the only treatment for 2,4 drops of butyl ester poisoning is recommended to alkalinize urine and symptomatic treatment. However, hemoperfusion may be effective too. Currently, there are few studies and no relevant literature references. We found through this study that hemoperfusion therapy has an exactly accurate curative effect on 2,4-dichlorophenoxyacetic acid central nervous toxicity.

Conclusions

To sum up, hemoperfusion therapy is a recommended method for emergency treatment of 2,4-dichlorophenoxyacetic acid poisoning patients compared with alkaline diuresis and treatment of complications, which can significantly reduce the central nerve injury of patients, promote the recovery of their consciousness, and significantly reduce the mortality rate. At present, the research on 2,4-dichlorophenoxyacetic acid poisoning is mainly focused on chronic reproductive toxicity, chronic nerve injury, and daily exposure. There is less research on acute poisoning. However, there are many acute poisoning patients of 2,4-dichlorophenoxyacetic acid in Qinghai, China, which should be paid

attention to. In general, the control group adopted routine treatment, which has a long recovery time for organ damage, and the mortality rate of moderate and severe patients is higher. Routine treatment has an effect on patients with mild poisoning. After active intervention, survival rate in the treatment group was greatly improved, with greatly reduced mortality rate, shortened hospitalization days, and achieved faster recovery of neurological damage. Hemoperfusion therapy treatment has a significant effect on the prognosis of patients and is worthy of promotion. Through the treatment outside and inside the hospital, the mortality rate of the patients was particularly low, but there were still some patients who have delayed treatment due to large dose of poison and long time during the way to hospital, resulting in the death of patients.

Conflict of Interests

The authors declare that they have no conflict of interest.

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