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Clinical analysis of penehyclidine hydrochloride combined with hemoperfusion in the treatment of acute severe organophosphorus pesticide poisoning

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ABSTRACT. This study aimed to observe the clinical curative effect of penehyclidine hydrochloride (PHC) combined with hemoperfusion in treating acute severe organophosphorus pesticide poisoning. We randomly divided 61 patients with severe organophosphorus pesticide poisoning into an experimental group (N = 31) and a control group (N = 30), and we compared the coma-recovery time, mechanical ventilation time, healing time, hospital expenses, and mortality between the two groups. The coma-recovery time, mechanical ventilation time, and healing time were lower in the experimental group than in the control group ($P < 0.05$), while the hospitalization expenses were higher in the experimental group than in the control group ($P < 0.01$); moreover, no significant difference was observed in the mortality rate between the two groups. Thus, PHC combined with hemoperfusion exerts a better therapeutic effect in acute severe organophosphorus pesticide poisoning than PHC alone.

Key words: Organophosphorus pesticide poisoning; Hemoperfusion; Penehyclidine hydrochloride

INTRODUCTION

Acute severe organophosphorus pesticide poisoning is a common critical disease in emergency room patients (Kumar et al., 2010; Chowdhary et al., 2014), which progresses rapidly and quickly leads to failure of the heart, lung, brain, and other organs, and subsequently, death (Jayawardane et al., 2012). The traditional method for the treatment of severe organophosphorus poisoning involves use of a cholinesterase reactivator (Eddleston et al., 2008; Tang et al., 2013). Although the combination of a cholinesterase reactivator and anticholinergic atropine has a poor effect (Buckley et al., 2011; Elsinghorst et al., 2013), a previous study has shown that use of atropine at an optimum dose can decrease the mortality rate (Biswas et al., 2013). However, atropine has a short half-life, requires administration of large dosages, and patients with severe poisoning require intravenous administration (Abedin et al., 2012); moreover, repeated administration at an interval of 2-10 min is required (Connors et al., 2013) and nursing of patients is tedious; furthermore, an appropriate dosage of atropine is not easy to determine; small dosages are not sufficient to achieve the therapeutic effect and large dosages can easily cause poisoning (Sharma et al., 2013). A previous study shows that penehyclidine hydrochloride (PHC) is a new generation cholinergic antagonist (Han et al., 2005) that can selectively act on M1, M3, N1, and N2 receptors, and can rapidly improve the muscarinic symptoms with a little effect on the heart rate. PHC can antagonize the nicotinic symptoms caused by excessive accumulation of acetylcholine in the neuromuscular junction of the striated muscle and can cross the blood-brain barrier to effectively control the severe convulsions, coma, and other symptoms of the nervous system induced by organophosphorus pesticide poisoning. PHC has a fast onset time, long half-life, is administered intramuscularly, excreted in low quantities by hemoperfusion adsorption, and does not require administration of high doses, which are ideal characteristics of a cholinolytic drug for the treatment of organophosphorus pesticide poisoning. PHC can only improve the symptoms of poisoning, but it does not eliminate the toxins from the body. Because of the high levels of toxins in patients with severe organophosphorus pesticide poisoning, the patients in critical condition may have to be hospitalized for a prolonged period, and they may even die. A recent study showed that hemoperfusion effectively removes the toxins of organic phosphorus pesticides from the extracorporeal circulation (Indira et al., 2013) by adsorption. The hemoperfusion apparatus effectively removes toxins from the poisoned blood, and the purified blood is transfused into the body, so that the health of the patients is quickly restored (Gil et al., 2010). In this study, we used PHC combined with hemoperfusion for the treatment of acute severe organophosphorus pesticide poisoning and observed the clinical effect. We observed a significant therapeutic effect, and we have described our findings below.

MATERIAL AND METHODS

General data

We enrolled 61 patients (30 men and 31 women) with acute severe organophosphorus pesticide poisoning admitted to the intensive care unit (ICU) of our hospital between December 2005 and January 2010; the ages of the patients ranged from 18 to 76 years (mean ± SD, 33.42 ± 7.46 years). The condition of these patients was diagnosed according to the diagnostic standard of the People's Republic of China, Ministry of Health, occupation with the risk of

organophosphorus pesticide poisoning. The pesticides that caused poisoning included phorate in 8 patients, parathion in 16 patients, dichlorvos DDVP in 11 patients, demeton in 10 patients, omethoate in 6 patients, trichlorfon in 7 patients, and malathion in 3 patients; in all patients, pesticide poisoning occurred via the oral route, which is the most common route of poisoning (Baydin et al., 2014). The doses of the organophosphorous pesticides were 50-500 mL. The treatment duration is 30 min to 4.5 h after medication. Cholinesterase activity (CHE) <30% at the hospital visit was defined as acute severe organophosphorus pesticide poisoning according to the diagnostic standard. Among the 61 patients, 42 were in coma, 46 had dyspnea, and 23 had shock in the first visit. Seven patients had cardiac arrest during treatment, which was successfully treated with advanced cardiopulmonary resuscitation (CPR).

Treatment methods

We randomly divided 61 patients into experimental group and control group. No significant difference was observed in the gender, age, clinical manifestation, and the levels and species of poisons between the two groups.

Gastric lavage was performed immediately after the diagnosis in patients in both groups using an automatic gastric lavage machine; 20,000-25,000 mL water was used as the gastric lavage fluid. Patients with coma were administered an appropriate application of mannitol to reduce brain edema, respiratory failure patients were managed by endotracheal intubation and mechanical ventilation, patients with shock were given antishock treatment, and patients with cardiac and respiratory arrest were treated with advanced CPR symptomatic treatment. Intravenous glucose tolerance test was performed, and all the patients were given 800-1200 mg pralidoxime iodide and 6 mg PHC by intramuscular injection; according to their condition, pralidoxime iodide was administered for 1-2 days and PHC was additionally administered. Hemoperfusion was administered to patients in the experimental group at the earliest using the continuous renal replacement therapy (Baxter, Germany) and disposable HA330-type resin hemoperfusion cartridge (Zhuhai Lizhu Medical Biological Materials Limited). A double-lumen catheter was inserted in the right femoral vein by venipuncture to set up a vascular channel; blood flow velocity, 160-200 mL/min and perfusion time, 120-150 min; the patients were perfused 1 or 2 times as per their condition. The patients were transferred from the ICU to the common ward when they regained consciousness and were successfully weaned from mechanical ventilation, had stable blood pressure, correction of shock, and stable vital signs.

The coma recovery time, mechanical ventilation time, healing time (CHE >60% and maintained above 24 h as healing), and hospitalization expenses of the two groups are shown in Table 1.

Table 1. Comparison of the awake time, mechanical ventilation time, healing time, and hospitalization expense between the two groups (means ± SD)

Group	Case	Awake time (day)	Mechanical ventilation time (day)	Healing time (day)	Hospitalization expense (yuan)
Experiment group	31	4.1 ± 2.2	3.8 ± 1.5	7.5 ± 2.4	29079 ± 2300
Control group	30	8.3 ± 1.4	6.8 ± 2.8	16.1 ± 2.8	18202 ± 1623

Statistical analysis

SPSS13.0 was used for statistical analysis; data are reported as means ± SD; the *t*-test was used for comparison between the two groups, and the ratios were compared using the chi-

square test; $P < 0.05$ was set as the statistically significance difference.

RESULTS

The coma-recovery time, mechanical ventilation time, and healing time in the experimental group were shorter than those in the control group, and the difference was statistically significant ($P < 0.05$); the hospital expenses of patients in the experimental group were higher than those of patients in the control group ($P < 0.05$; Table 1). The mortality rate of patients in the experimental group was 19.4% (6/31) and that of patients in the control group was 16.7% (5/30); no significant difference was observed in the mortality rates between the two groups ($P > 0.05$).

DISCUSSION

The mechanism of organophosphorus pesticide poisoning involves entry of the organophosphorus pesticide into the body and combination with cholinesterase to form a stable phosphorylated cholinesterase, which cannot be broken down by acetylcholine, and thus, leads to accumulation of large amounts of phosphatidylcholine in the body and causes muscarinic, nicotinic, and central nervous system symptoms (Karami-Mohajeri et al., 2014), simultaneously with changes in the peripheral nervous system (Jayasinghe et al., 2012). In addition, bullous dermatitis and other rare manifestations are also observed (Dong et al., 2013). The traditional method for treating organophosphorous poisoning involves the uses of a cholinesterase reactivator combined with atropine; however, this treatment does not eliminate the poison absorbed in the body, which results in damage to the heart, lung, brain, kidney, and other multiple organ damage or death (Elsinghorst et al., 2013). Hemoperfusion rapidly clears the poison from the blood via extracorporeal circulation and adsorption and easily adsorbs high molecular weight and fat-soluble poisons that can bind with proteins, especially those with the hydrophobic lipophilic group. Organophosphorus pesticide is fat-soluble and hydrophobic substances, after entering into the blood, mostly bind with the lipoprotein, so that hemoperfusion can clear away the poison entering the body. In addition, a previous animal study confirmed that antioxidants also can alleviate the organophosphorus pesticide poisoning (Shokrzadeh et al., 2012).

Our study shows that coma-recovery time, mechanical ventilation time, and healing time were significantly shorter in the experimental group than in the control group, which suggested that hemoperfusion effectively removed the organophosphorus poisons from the body, and thus, decreased the organ damage and shortened the course of the disease. The following factors should be considered during hemoperfusion: 1) time of treatment: the best treatment effect is observed within 6 h of poisoning, because the poison reaches its peak blood concentration in this time and subsequently may exist in the free state, which ensures the highest removal efficiency; 2) repeated perfusion: in the case of severe organophosphorus pesticide poisoning, a large quantity of poison enters the body in a few hours (up to 24 h) after blood perfusion, and the poisons distributed in the adipose tissue can diffuse into the blood through the intestinal tissue space, viscera, and muscle, and thus, increase the blood concentration of the poison and aggravate the clinical symptoms. Therefore, hemoperfusion should be repeated according to the condition of the patient. Previous studies have shown that the adsorbent surface approaches saturation after 2 h of perfusion and decreases the rate of toxin removal, and thus, increasing the perfusion time does not increase the clearance; 3) treatment of hypotension: hypotension is common in patients with severe organophosphorus pesticide poisoning,

and thus, treatment should be administered to patients in the head-down position, and active fluid infusion should be administered to expand blood volume; treatment to increase blood pressure should be administered, when necessary, to maintain systolic blood pressure above 90 mmHg; the blood flow velocity should be decreased during hemoperfusion. Hemoperfusion should not be forbidden in patients with hypotension. Otherwise, the optimal treatment time will be delayed. Although hemoperfusion treatment has a curative effect, it only removes the poison, but it does not correct the pathophysiological changes caused by the organophosphorus pesticide; therefore, hemoperfusion is performed in combination with treatment with anticholinergic drugs and cholinesterase agents, and other comprehensive treatment measures should be taken to support the respiratory and circulatory function (Hu et al., 2014). All patients in our study completed the hemoperfusion treatment and were successfully treated for lowering of the intracranial pressure and cerebral edema, were weaned from ventilator support, and received antishock treatment.

PHC, a new anticholinergic drug, has selective anticholinergic effects, mainly on the M1 and M3 receptor, has little effect on the heart rate, is administered in small doses and thus does not require repeated administration; therefore, it has lower toxicity than atropine, and combination of PHC with cholinesterase reactivators may have a better curative effect than the combination of atropine with the cholinesterase reactivators. Clinically, PHC has the following advantages over atropine: 1) it can be administered in small doses and is rapidly absorbed via intramuscular injection, which can exert its effect 10-15 min after injection, and has a long half-life ($t_{1/2}$ = 10.4 h), which eliminates the need for frequent drug use; 2) it has obvious selectivity for the M receptor, which can effectively reduce the toxicity of anticholinergic drugs on the heart; it is associated with a low rate of poisoning; and 3) the use of PHC is easy to master, which has rare side effects.

Application of PHC combined with hemoperfusion in the treatment of acute severe organophosphorus pesticide poisoning can significantly reduce organ injury, have a curative effect, shorten the course of treatment, and improve the quality of life of patients. However, the treatment is expensive, and thus, this treatment is used by a limited number of patients. Further studies are required to address this issue so that this treatment can be widely used.

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