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Clinical efficacy of intravenous infusion of atropine with micropump in combination with hemoperfusion on organophosphorus poisoning

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ABSTRACT

Objective: To observe the clinical efficacy of intravenous infusion of atropine with micropump in combination with hemoperfusion on organophosphorus poisoning patients, and investigate the potential mechanism.

Methods: In this study, we enrolled 136 organophosphorus poisoning patients who received treatment in this hospital between January 2009 and December 2017, and they were divided into three groups according to the clinical treatment methods, i.e. Group A (comprehensive treatment with HP, n = 47), Group B (continuous intravenous infusion of atropine with micropump, n = 43) and Group C (regular intravenous infusion of atropine, n = 46). In addition to the close monitoring of vital signs, we recorded the atropinization time (min), cholinesterase reactivation time (h), total dose of atropine, recurrence, incidence rate of atropine poisoning (%), hospitalization time (d) and cure rate (%).

Results: In comparison with Group C, patients in Group A and B manifested more stable vital signs with lower total dose of atropine and incidence rate of atropine poisoning and shorter cholinesterase reactivation time, while the cure rate was remarkably increased ($p < 0.05$), and no significant differences were observed in atropinization time among three groups ($p > 0.05$). Compared to Group B and C, total dose of atropine in Group A was significantly decreased with obvious excellence in hospitalization time, reduction of complications and increases in cure rates ($p < 0.05$). Moreover, patients in Group A had the lowest mortality rate among three groups.

Conclusion: In treatment of organophosphorus poisoning patients, HP and continuous intravenous infusion of atropine using micropump can elevate the survival rate, reduce the incidence of adverse reaction, shorten the reactivation time of cholinesterase and decrease the incidence rate of complications, which are superior to the traditional treatment method.

1. Introduction

Organophosphorus pesticide, a kind of organophosphorus ester, can cause acute poisoning in case of excessive exposure or accident administration. Organophosphorus poisoning is an acute clinical emergency with mild symptoms like dizziness, fatigue, and in some severe cases, patients may exhibit loss of consciousness, paroxysmal convulsion, central respiratory failure or even death. Currently, major treatment methods include intravenous infusion of atropine and hemoperfusion (HP). Atropine is preferred in treatment of organophosphorus poisoning, and correct use of atropine plays a key role in treatment. HP is a kind of blood purification technique that can eliminate the toxins inside the body using surface adsorbent, and literatures have reported that it can improve the success rate of treatment for organophosphorus poisoning (Gunnell et al., 2007; Li and Lu, 2011). To analyze the clinical efficacy of continuous intravenous infusion of atropine using atropine and HP on the acute organophosphorus poisoning, we enrolled 136 organophosphorus poisoning patients who were treated in this hospital between January 2009 and December 2017 as subjects for retrospective study, and detailed information is reported as follows.

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2. Data and methods

2.1. Subjects

We enrolled 136 organophosphorus poisoning patients who were treated in this hospital between January 2009 and December 2017, in which there were 60 males and 76 females aged between 14 and 78 years old with an average of (47.3 ± 7.5) years old. At admission, activity of cholinesterase was less than 500 U (normal range: 4500 – 10,500 U), and patients manifested symptoms like decreased heart rate, salivation and skin clamminess. Patients with metabolic diseases, heart diseases or endocrine diseases were excluded. Among these patients, there were 18 patients in deep coma, and 108 patients with severe vomiting, diarrhea and abdominal pains. After treatment, 119 patients recovered and 17 patients died. In this study, diagnoses of 136 patients were made as per the following criteria of organophosphorus poisoning: (1) poisoning history (oral administration of organophosphorus pesticide or exposure to organophosphorus pesticide); (2) typical symptoms or vital signs of poisoning; (3) decreased activity of cholinesterase in whole blood; (4) detectable organophosphorus or its metabolite in the content of blood or stomach.

2.2. Methods

2.2.1. Grouping

136 patients were divided into three groups according to their treatment: 47 patients underwent comprehensive treatment plus HP, Group A; 43 underwent continuous intravenous infusion of atropine using micropump, Group B; 46 underwent regular intravenous infusion of atropine, Group C. Comparisons of the general data among three groups showed that differences had no statistical significance ($p > 0.05$), suggesting that data were comparable (Table 1).

2.2.2. Treatment

Organophosphorus poisoning patients in three groups underwent regular urinary catheterization, skin cleaning, thorough gastric lavage, rapid atropinization and application of pralidoxime chloride; patients took diuretic or mannitol to promote the excretion of toxin for prophylaxis of encephaledema; symptomatic treatment was conducted for preventing the infection and protecting the gastric mucosa; for patients with respiratory failure, trachea cannula or tracheotomy was adopted with mechanical ventilation. Regular treatment included the regular administration of pyraloxime iodide. Two venous accesses were established, one for administration of atropine (5 mg/mL), and the other for comprehensive treatment with cholinesterase reactivators, anti-infection therepy, transfusion and nutrition support through veins.

For patients in Group A, atropinization maintenance was conducted with HP: Frese-nius 4008 dialysis machine and HA230 resin hemoperfusion apparatus (Livzon Pharmaceutical Group Inc.) were applied in the temporarily established dialysis access in femoral veins in velocity of 100 to 200 mL/min for 2 h of persistent perfusion. Perfusion times depended on the poisoning condition of patients, and, for severe cases, perfusion was conducted twice per day, which was changed into once per day. During treatment, regular administration of atropine was conducted to maintain the atropinization.

Patients in Group B received medication through continuous intravenous infusion using micropump: Firstly, patients received the rapid intravenous injection of atropine at dose of 10 to 20 mg/-time, and each time of administration lasted for 5 to 10 min until atropinization; then, atropine was used through continuous intravenous infusion using micropump, and the dose depended on the total dose of atropine before atropinization; through calculation, atropine was administrated in dose ranging from 0.0165 to 0.0281 mg/min/kg through continuous intravenous injection using micropump to sustain the effective concentration of atropine in blood; during the medication of atropine, changes in disease condition were monitored closely for adjustment of atropine dose at any time.

Patients in Group C underwent regular intravenous injection: According to the medical advice, drugs were administrated intravenously, once every 10 or 30 min, or 1 or 2 h; based on the changes in vital signs of patients and the examination of cholinesterase, dose was adjusted at any time to maintain the atropinization for 2 to 3 days, so as to prevent the recurrence of organophosphorus poisoning.

2.2.3. Observation indexes

In addition to the close monitoring of vital signs, we recorded the atropinization time (min), cholinesterase reactivation time (h), total dose of atropine, recurrence, incidence rate of atropine poisoning (%), hospitalization time (d) and cure rate (%).

2.3. Statistics

SPSS 17.0 software was applied for statistical analysis. Measurement data were presented in mean ± standard deviation (SD), and t test was carried out for intergroup comparison. Qualitive data were compared with chi-square test. $p < 0.05$ suggested that difference had statistical significance.

3. Results

3.1. Comparison of the vital signs among three groups

Stable vital signs were only observed in Group A and B, and significant differences were identified in comparisons between Group C and Group A, B ($p < 0.05$; Table 2).

3.2. Comparison of the efficacy on patients among three groups

In comparison with Group C, dose of atropine, time of cholinesterase reactivation and incidence rate of atropinism were decreased in Group A and B with an increase in cure rate ($p < 0.05$), but there was no evident change in the atropinization time ($p > 0.05$). Compared to Group B and C, total dose of atropine in Group A was significantly decreased with obvious excellence in hospitalization time, reduction of complications and increases in cure rates ($p < 0.05$). Moreover, patients in Group A had the lowest mortality rate among three groups (Table 3).

Table 1
Comparison of the general data among three groups ($\bar{x} \pm s$).

Group	Gender (male/female)	Age (years)	Toxic dose (mL)	Toxic time (h)
Group A	19/28	46.6 ± 6.9	50.4 ± 16.5	1.3 ± 0.6
Group B	16/27	48.4 ± 8.0	49.0 ± 14.4	1.2 ± 0.7
Group C	17/29	44.3 ± 6.5	51.3 ± 15.7	1.5 ± 0.4

Table 2
Comparison of the vital signs among three groups ($\bar{x} \pm s$).

Group	n	Heart rate (beat/min)	Pupil (mm)	Flushing	Temperature (°C)
Group A	47	102 ± 4.8	4.5 ± 0.4	++	37.7 ± 0.6
Group B	43	106 ± 7.5	4.3 ± 0.6	++	38.0 ± 0.3
Group C	46	115 ± 12.9[a]	5.2 ± 0.7[a]	++++	38.6 ± 0.4[a]

Note: [a]$p < 0.05$ *vs.* Group A or B.

Table 3
Comparison of the efficacy on patients among three groups.

Group	n	Atropine application		Complications		Cholinesterase reactivation time	Length of stay in hospital (d)	Cure rate (%)
		Atropinization time (min)	Total dose (mg)	Recurrence [n (%)]	Atropinism [n (%)]			
Group A	47	183.5 ± 22.9	131.3 ± 34.3	3(6.4%)	3(6.4%)	9.2 ± 4.4	7.5 ± 3.4	100
Group B	43	174.5 ± 72.9	214.9 ± 18.4	3(7.0%)	3(7.0%)	9.6 ± 8.3	9.9 ± 4.6	88.4
Group C	46	196.9 ± 87.5	283.3 ± 17.5	9(19.6%)	14(30.4%)	13.2 ± 6.5	10.8 ± 3.8	69.6

4. Discussion

Organophosphorus poisoning with a high incidence rate in clinical acute poisoning diseases severely affects the patients and their family, and how to improve the efficacy on organophosphorus poisoning has remained a major problem nowadays. Atropine, classic drug in treatment of organophosphorus poisoning, is a kind of anticholinesterase drugs that can block the muscarinic acetylcholine receptor in the effector dominated by the cholinergic nerves, thus eliminating the muscarinic and central nerve system symptoms, relieving the spasm in smooth muscle, inhibiting the secretion of gland and keeping the airway open. However, organophosphorus can has a long-term effect on cholinesterase. In treatment of organophosphorus poisoning, due to the rapid metabolism of atropine, intravenous infusion of atropine takes effect within 1 to 4 min, and the peak level is attained at 8 min which will be diminished at 18 min and totally disappear at about 1 h (Gu et al., 2008; Yan et al., 2010). Thus, optimal detoxification effect can hardly be obtained in treatment with less dose of atropine, but excessive use results in atropinism (Shi et al., 2005). Hence, appropriate dose of atropine can attain the atropinization, and also avoid the outcome of excessive use, as well as the recurrence caused by reduction or early withdrawal of atropine after atropinization.

In this study, we found that the efficacy of HP in patients taking continuous intravenous infusion using micropump is superior to the intravenous pump. As shown in Table 2, patients in Group A and B showed more stable vital signs than those in Group B, while Table 3 showed that in Group A and B, the total dose of atropine, cholinesterase reactivation time and incidence rate of atropinism were reduced or shortened with an elevated cure rate. Due to the difficulty in attaining the equilibrium between the intake and elimination rates of atropine through regular intravenous infusion, patients are more susceptible to the fluctuation in blood concentration; moreover, at the time of attaining peak levels, they may exhibit flushing, accelerated heart rate, excitation in sympathetic nerve, increase in oxygen consumption, while at the low level, perspiration or shrinkage of pupil may emerge, thus affecting the accurate evaluation, and contributing to the atropinism or even death. With the advantage of pumping atropine at a stable rate, intravenous infusion using micropump can sustain the equilibrium between the drug intake and elimination rates, thereby giving rise to the homeostasis in blood concentration and minimizing the possibility of atropinization at the peak level or even atropinism. It is also reported that this method can attain more stable vital signs than the regular intermittent intravenous infusion, while sustaining the stable blood concentration with little changes in disease condition; moreover, it is convenient to use the micropump to adjust the dose, and for patients requiring adjustment, pumping rate can be easily modulated through the pump, which can alter the dose easily while reduce the nursing work (Lotti, 2001; Munidasa et al., 2004). In addition, intravenous infusion of atropine with micropump shows advantages in terms of mortality rate, atropinism, intermediate syndrome of organophosphorus poisoning and recurrence rate (Yang and Liu, 2002). Thus, it not only provides conditions and guarantee for scientific medication of atropine, but also reduces the drug contamination due to multiple injection, adjust the dose of atropine and improves the success rate of rescue with relief in nursing load. Thus, it is worthy of being promoted in clinical practice.

HP, a clinical dialysis technique in rescue of drug or toxin poisoning, can drain the blood of patients through *in-vitro* circulation into the hemoditoxifier containing the broad-spectrum absorbent, through which it can eliminate the endogenous or exogenous toxins rapidly for blood purification and disease treatment (Zhao et al., 2003). Currently, HP has gained promising effect in treatment of acute and critical organophosphorus poisoning. For patients with critical organophosphorus poisoning, HP is the preferred method for blood purification, in which organophosphorus with relative molecular weight of 584,600 can bind to the proteins in the blood, thus forming macromolecules; while HP is excellent in eliminating the macromolecular toxins with lipid solubility. Thus, in organophosphorus poisoning patients, HP can rapidly clear the organophosphorus in blood, thereby blocking the binding with cholinesterase, improving the survival rate of patients, and reducing the incidence of complications and recurrence. Currently, HP remains an effective method, and, especially for organophosphorus poisoning, it can reduce the intermediate syndrome and atropine dose, shorten the length of stay in hospital, increase the success rate of treatment and decrease the mortality rate (Eddleston et al., 2004; Johnson et al., 2000). A study has indicated that HP can also evidently correct the low response to atropine in organophosphorus poisoning (Peter et al., 2006), which is also observed in this study. Literature (Rahimi et al., 2006) has proved that after one time of HP, poisoning patients can experience a reduction of 30% to 50% in the toxin concentration. With a high lipid solubility, organophosphorus pesticide could reach a concentration in lipid tissues that is 20 to 50 times that of the blood concentration, and after absorption, it can be delivered into the fat tissues spread in the body, thus causing continuous damage for constant exchange with blood (Pawar et al., 2006). Thus, multiple HPs can thoroughly eliminate the toxins, but the application of HP is limited for its failure in recovering the activity of cholinesterase due to its inability to correct the pathophysiological changes caused by toxins (Eddleston et al., 2009). Hence, only HP in combi-

nation with atropine and cholinesterase reactivator can exert the excellent efficacy.

5. Conclusion

Thus, in treatment of organophosphorus poisoning patients, HP and continuous intravenous infusion of atropine using micropump can elevate the survival rate, reduce the incidence of adverse reaction, shorten the reactivation time of cholinesterase and decrease the incidence rate of complications, which are superior to the traditional treatment method.

References

Eddleston, M., Buckley, N.A., Checketts, H., Senarathna, L., Mohamed, F., Sheriff, M. H., 2004. Speed of initial atropinisation in significant organophosphorus insecticide poisoning: a systematic comparison of recommended regimens. J. Toxicol. Clin. Toxicol. 42, 865–875.

Eddleston, M., Eyer, P., Worek, F., Juszczak, E., Alder, N., Mohamed, F., 2009. Pralidoxime in acute organophosphorus insecticide poisoning: a randomised controlled trial. Plos Med. 6, e1000104.

Gu, H.Z., Liu, S.Z., Jin, W.Y., Zhu, W., Zhu, H.Y., Yang, J., 2008. Comparison of three different administration methods of pralidoxime chlorine in the treatment of acute organophosphorus insecticide poisoning. Chin. J. Crit. Care Med. 28, 110–112.

Gunnell, D., Eddleston, M., Phillips, M.R., Konradsen, F., 2007. The global distribution of fatal insecticide self-poisoning: systematic review. BMC Public Health 7, 357.

Johnson, M.K., Jacobsen, D., Meredith, T.J., 2000. Evaluation of antidotes for poisoning by organophosphorus insecticides. Emerg. Med. 12, 22–37.

Li, M.F., Lu, Z.Q., 2011. Clinic research of acute organophosphorus insecticide poisoning. Chin. J. Ind. Hyg. Occup. Dis. 29, 636–639.

Lotti, M., 2001. Clinical toxicology of anticholinesterase agents in humans. In: Handbook of insecticide toxicology. San Diego: Academic Press, pp. 1043–1085.

Munidasa, U.A., Gawarammana, I.B., Kularatne, S.A., Kumarasiri, P.V., Goonasekera, C.D., 2004. Survival pattern in patients with acute organophosphate poisoning receiving intensive care. J. Toxicol. Clin. Toxicol. 42, 343–347.

Pawar, K.S., Bhoite, R.R., Pillay, C.P., Chavan, S.C., Malshikare, D.S., Garad, S.G., 2006. Continuous pralidoxime infusion versus repeated bolus injection to treat organophosphorus insecticide poisoning: a randomised controlled trial. Lancet 368, 2136–2141.

Peter, J.V., Moran, J.L., Graham, P., 2006. Oxime therapy and outcomes in human organophosphate poisoning: an evaluation using meta-analytic techniques. Crit. Care Med. 34, 502–510.

Rahimi, R., Nikfar, S., Abdollahi, M., 2006. Increased morbidity and mortality in acute human organophosphate-poisoned patients treated by oximes: a meta-analysis of clinical trials. Hum. Exp. Toxicol. 25, 157–162.

Shi, H.W., Tong, F., Tian, Y.P., 2005. Standardized therapy for acute organophosphate poisoning. Chin. J. Emerg. Med. 14, 351–352.

Yan, Y.J., Li, X.J., Ning, G.Y., Zhao, X.B., Pan, Y.F., Yan, X.Y., 2010. Clinical trial on standard treatment of acute organophosphorus poisoning. Chin. J. Ind. Hyg. Occup. Dis. 28, 321–324.

Yang, J., Liu, K.Q., 2002. 1403 cases of death analysis for acute organophosphorus insecticide poisoning in China. Chin. J. Intern. Med. 41, 620–621.

Zhao, D.L., Guan, L., Wang, H.B., 2003. The domestic application of oxime in the treatment of organophosphorus insecticide poisoning. Chin. J. Emerg. Med. 12, 382–383.