

Protective effects of scopolamine and penehyclidine hydrochloride on acute cerebral ischemia-reperfusion injury after cardiopulmonary resuscitation and effects on cytokines

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Abstract. The objective of this study was to investigate the protective effects of scopolamine and penehyclidine hydrochloride on acute cerebral ischemia-reperfusion injury after cardiopulmonary resuscitation, and the effect on cytokine levels. Eighty patients with cardiac arrest admitted to our hospital from June 2011 to December 2015 were recruited and randomly divided into two groups (n=40 each). Following cardiopulmonary resuscitation, scopolamine was administered in the control group, whereas penehyclidine hydrochloride was administered in the observation group. After intervention, the following medical indicators were compared between the groups: Intracranial pressure, cerebral oxygen partial pressure, cerebral perfusion pressure, assessment of the balance of cerebral oxygen supply and demand, levels of neuron-specific enolase (NSE) and blood lactic acid, levels of oxidative stress markers, and levels of inflammatory-related factors. Additionally, the areas of brain tissue edema and National Institutes of Health Stroke Scale (NIHSS) scores before and after intervention were compared. Rescue success rates of the groups were recorded. After intervention, the following indicators were lower in the observation group than in the control group: Intracranial pressure (p<0.05), levels of NSE (p<0.05), levels of blood lactic acid (p<0.05), levels of malondialdehyde (p<0.05), and levels of interleukin 6 (IL-6), tumor necrosis factor- α , IL-1, and hs-CRP (p<0.05). However, the following indicators were higher in the observation group than in the

control group: Cerebral oxygen partial pressure, cerebral perfusion pressure (p<0.05), levels of CaO₂, CjvO₂, and CERO₂ (p>0.05), and levels of superoxide dismutase and glutathione peroxidase (p<0.05). Additionally, the areas of brain tissue edema after intervention were smaller in the observation group than those before intervention and those after intervention in the control group (p<0.05). Similarly, the NIHSS scores after intervention in the observation group were lower than those before intervention and those after intervention in the control group (p<0.05). Rescue success rate was significantly higher in observation group than in control group (p<0.05). In conclusion, administration of penehyclidine following cardiopulmonary resuscitation can effectively improve cerebral perfusion pressure, lower intracranial pressure, reduce brain tissue edema and inflammation, and improve neurological function.

Introduction

Cardiopulmonary resuscitation refers primarily to a procedure involving repeated chest compressions and artificial respiration in an attempt to maintain the circulation of a patient suffering from respiratory or cardiac arrest resulting from any cause (1). Respiratory and cardiac arrest are among the most critical clinical conditions, for which treatment is a race against time (2). This is especially true for older patients with significantly declined body functions that result in high sensitivity and poor tolerance to hypoxia. It was confirmed that (3,4) both spontaneous respiration and the heartbeat can be restored in some older patients with cardiac and respiratory arrest, if it is detected early, and treated immediately and appropriately. Early detection and immediate and appropriate treatment can reduce the impact of respiratory and cardiac arrest on the functions of key organs, and is therefore the key to a successful rescue. The recovery rate of cerebral resuscitation in the basic stage of cardiopulmonary resuscitation is relatively low, while the efficiency of cerebral resuscitation is closely related to the prognosis and quality of life of patients (5). Therefore, procedures that can effectively improve the efficiency of cardiopulmonary resuscitation, especially the result of cerebral resuscitation, are of

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great significance in increasing the success rate of rescue, and improving the prognosis of patients (6). Scopolamine is a medication used in the treatment of cardiac arrest. Its clinical value for improving spontaneous circulation and the success rate of resuscitation have been recognized. However, long-term use of scopolamine can lead to decreased secretion, dysuria, and excessive vascular dilatation. Importantly, it has a negative effect on cerebral resuscitation in patients on advanced life support (7). Penehyclidine is currently the most commonly used anticholinergic drug, and is primarily administered for rescue from organophosphorus pesticide poisoning. Its application in cardiopulmonary resuscitation is less well understood. In this study, the two drugs were assessed and compared for their effects in cardiopulmonary resuscitation.

Patients and methods

Patients. Eighty patients with cardiac arrest admitted to Clinical Medicine Skill Center from June 2011 to December 2015 were recruited in this study. All patients were diagnosed with sudden cardiac arrest resulting from acute myocardial infarction. Patients were diagnosed according to clinical symptoms and ECG. Patients with other conditions such as severe liver and kidney dysfunction, chronic respiratory diseases, neurological diseases, previous cardiopulmonary surgery, mental illness, coagulation disorders, and congenital heart disease were excluded. A consent form was signed by the patient's families before recruitment, and the study was approved by the Ethics Committee of Jining Medical University (Shandong, China). The patients were randomly and equally divided into two groups, with 40/group. Among the two groups, the observation group included 23 males and 17 females, aged 50-70 years, with an average age of 62.3 ± 2.1 years, who underwent cardiopulmonary cerebral resuscitation from 15 sec to 15 min, with an average of 3.1 ± 0.2 min post-cardiac arrest. The control group included 24 males and 16 females, aged 50-70 years, with an average age of 62.4 ± 2.0 years, who underwent cardiopulmonary cerebral resuscitation from 15 sec to 15 min, with an average time of 3.0 ± 0.2 min post-cardiac arrest. There were no significant differences in sex, age, or the time from cardiac arrest to implementation of cardiopulmonary cerebral resuscitation between the two groups ($p > 0.05$).

Methods. Cardiopulmonary resuscitation was performed on all participants in accordance with the 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation. Tracheal intubation was performed promptly by anesthetists, and ventilation was achieved either through artificial ventilation or ventilator-assisted ventilation. Different drugs were chosen and administered depending on the efficiency of cardiopulmonary resuscitation, including atropine, adrenaline, sodium bicarbonate, calcium gluconate, norepinephrine, and other vasoactive agents. When spontaneous heartbeat was restored, patients in the control group were administered scopolamine (CFDA approval no. H33021707 granted to Hangzhou Minsheng Pharmaceutical Co., Ltd., Hangzhou, China). First, a 40 mg bolus of the drug was administered via

intravenous injection, followed by an additional 80 mg administered by an intravenous infusion pump for 24 h. Patients in the observation group were administered penehyclidine hydrochloride (CFDA approval no. 0060H2620 granted to Chengdu List Pharmaceutical Co., Ltd., Chengdu, China). First, a 2 mg bolus of the drug was administered via intravenous injection, followed by an additional 4 mg administered by an infusion pump for 24 h.

Medical indicators. After intervention, the following medical indicators were compared between the two groups: Intracranial pressure, cerebral oxygen partial pressure, cerebral perfusion pressure (CPP), assessment of the balance of cerebral oxygen supply and demand, levels of neuron-specific enolase (NSE) and blood lactic acid, levels of oxidative stress markers, and levels of inflammatory-related factors. In addition, the areas of brain tissue edema and the National Institutes of Health Stroke Scale (NIHSS) scores before and after intervention were compared. Rescue success rates of two groups were recorded.

Criteria of indicators. For measurement of intracranial indicators, lumbar puncture and lumbar cistern intubation were performed on patients to measure intracranial pressure, and cerebral oxygen partial pressure was measured by a cerebral oxygen partial pressure probe. Simultaneously, a pressure sensor was connected. The CPP was the difference between mean arterial blood pressure and intracranial pressure. Blood gas analysis was performed on radial artery and jugular venous blood collected from the patients. With a specific formula, the data were used to calculate arterial oxygen content (CaO_2), venous oxygen content (CjvO_2), the difference between arterial and venous oxygen content (Da-jvO_2), and cerebral oxygen uptake rate (CERO_2). The levels of NSE were measured by enzyme-linked immunosorbent assay (ELISA; reference values below 12.5 U/ml). The levels of lactic acid were determined by neutralization titration [reference values from 0.5-1.7 mmol/l (5-15 mg/dl)]. The immunoassay kit and lactic acid assay kit were from Shanghai Huamei Biology Co., Ltd. (Shanghai, China). The levels of malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px) in blood were measured by spectrophotometry, enzyme rate assay, and colorimetric assay, respectively. The adult reference values for MDA, SOD, and GSH-Px were 3.52-4.78 nmol/ml, 242-620 U/l, and 26-34 U/l, respectively. The levels of all inflammation-related factors were determined by ELISA, including tumor necrosis factor- α (TNF- α) (adult reference values, 1-10 ng/ml), IL-1 (adult reference values, 130-250 ng/ml), IL-6 (adult reference values, 67.37-150.33 ng/l), and hs-CRP (adult reference values, <10 mg/l). Neurological function was assessed using NIHSS scores, with a maximum score of 42 points among 11 items. The area of brain tissue edema before and after intervention was measured using head magnetic resonance imaging (MRI) by two radiologists in conjunction who each had over 5 years of experience in operating and interpreting MRI.

Statistical analysis. SPSS 13.0 statistical software (IBM Corp., Armonk, NY, USA) was used for data analysis. Numerical

Table I. Intracranial pressure, cerebral oxygen partial pressure and CPP after intervention.

Groups	Intracranial pressure (mmHg)	Cerebral oxygen partial pressure (mmHg)	CPP (mmHg)
Observation (n=40)	17.6±3.2	23.1±2.4	66.1±10.9
Control (n=40)	20.3±4.1	21.6±2.1	61.3±9.3
t-test	3.283	2.975	2.119
P-value	0.002	0.004	0.037

CPP, cerebral perfusion pressure.

Table II. Supply and demand of brain oxygen after intervention.

Group	CaO ₂ (ml/l)	CjvO ₂ (ml/l)	CERO ₂ (ml/l)
Observation (n=40)	165.1±23.1	113.5±16.1	35.6±5.6
Control (n=40)	152.3±21.3	105.9±14.6	31.1±4.0
t-test	2.576	2.212	4.136
P-value	0.012	0.030	<0.001

CaO₂, arterial oxygen content; CjvO₂, venous oxygen content; CERO₂, cerebral oxygen uptake rate.

Table III. Levels of NSE and blood lactic acid after intervention.

Group	NSE (U/ml)	Blood lactic acid (mmol/l)
Observation (n=40)	16.1±0.2	1.2±0.1
Control (n=40)	25.5±1.1	1.9±0.3
t-test	53.174	14.000
P-value	<0.001	<0.001

NSE, neuron-specific enolase.

data are presented as mean ± standard deviation. The t-test was used for comparisons of mean values between the two groups. The χ^2 test was used for comparisons of ratios between the two groups. P<0.05 was considered to indicate a statistically significant difference.

Results

Intracranial pressure, cerebral oxygen partial pressure, and CPP after intervention. After intervention, intracranial pressure was lower (p<0.05), while cerebral oxygen partial pressure and CPP were higher (p<0.05) in the observation group than in the control group (Table I).

Supply and demand of brain oxygen after intervention. After intervention, the levels of CaO₂, CjvO₂, and CERO₂ were higher in the observation group than in the control group (p>0.05) (Table II).

Table IV. Levels of oxidative stress markers after intervention.

Group	MDA (nmol/ml)	SOD (U/l)	GSH-Px (U/l)
Observation (n=40)	3.6±0.2	378.5±26.6	38.0±4.2
Control (n=40)	7.1±1.0	195.0±11.4	21.2±3.1
t-test	21.706	40.102	20.354
P-value	<0.001	<0.001	<0.001

MDA, malondialdehyde; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase.

Table V. Levels of inflammation-related factors after intervention.

Group	IL-6 (ng/l)	TNF- α (ng/ml)	IL-1 (ng/l)	hs-CRP (mg/l)
Observation (n=40)	34.6±6.1	12.1±0.2	0.61±0.1	10.5±1.0
Control (n=40)	153.2±14.1	18.3±0.5	0.93±0.2	31.1±2.0
t-test	48.825	72.815	9.051	58.266
P-value	<0.001	<0.001	<0.001	<0.001

IL, interleukin; TNF- α , tumor necrosis factor- α .

Levels of NSE and blood lactic acid after intervention. After intervention, the levels of NSE and blood lactic acid were lower in the observation group than in the control group (p<0.05) (Table III).

Levels of oxidative stress markers after intervention. After intervention, the levels of SOD and GSH-Px were higher (p<0.05), while the levels of MDA were lower (p<0.05) in the observation group than in the control group (Table IV).

Levels of inflammation-related factors after intervention. After intervention, the levels of IL-6, TNF- α , IL-1, and hs-CRP were lower in the observation group than in the control group (p<0.05) (Table V).

Area of brain tissue edema before and after intervention. There was no significant difference in the area of brain tissue edema between the two groups before intervention (p>0.05). The areas of brain tissue edema in the observation group were smaller than those before intervention, and those of the control group after intervention (p<0.05) (Table VI).

NIHSS score before and after intervention. There were no significant differences in NIHSS scores between the two groups before intervention (p>0.05). The NIHSS scores after intervention in the observation group were lower than those before intervention, and those in the control group after intervention (p<0.05) (Table VII).

Comparison of successful rescue rate between two groups. There were 38 cases of successful rescue in observation group

Table VI. Area of brain tissue edema before and after intervention.

Group	Area before intervention (cm ²)	Area after intervention (cm ²)	t-test	P-value
Observation (n=40)	4.0±0.3	2.0±0.1	40.000	<0.01
Control (n=40)	4.1±0.3	3.5±0.3	8.944	<0.01
t-test	0.981	30.000	-	-
P-value	0.121	<0.01	-	-

Table VII. NIHSS score before and after intervention.

Group	Before intervention (points)	After intervention (points)	t-test	P-value
Observation (n=40)	23.5±3.3	10.3±1.1	24.000	<0.01
Control (n=40)	23.5±3.4	19.5±2.4	6.079	<0.01
t-test	<0.01	22.039	-	-
P-value	1.000	<0.01	-	-

NIHSS, National Institutes of Health Stroke Scale.

(95.0%) and 28 cases in control group (70.0%). Success rate of rescue in observation group was significantly higher than in control group ($\chi^2=7.013$; $p=0.008$).

Discussion

With the widespread procedures for cardiopulmonary resuscitation and the knowledge of public medical emergencies, some patients with cardiac arrest can be effectively rescued before hospital admission (8). Patients who suffer from cardiac arrest can also be rescued with a high success rate (9). The recovery rate of cerebral resuscitation in the basic stage of cardiopulmonary resuscitation is relatively low, while the efficiency of cerebral resuscitation is closely related to prognosis and the quality of life of patients. Presently, the most effective procedures to rescue patients with cardiac arrest include chest compression, tracheal intubation to assist breathing, head cooling, and other supporting treatments for cardiopulmonary cerebral resuscitation (10). When the aforementioned cardiopulmonary resuscitation procedures are performed on patients with sudden respiratory and cardiac arrest, drugs should also be administered to increase the success rate of rescue, improve the outcome of cerebral resuscitation, and further improve patient prognosis (11-13).

In this study, the effects of scopolamine and penehyclidine hydrochloride on the prevention and treatment of acute cerebral ischemia-reperfusion injury after cardiopulmonary resuscitation were investigated. It was found that after drug intervention, intracranial pressures were lower, while other indicators including the cerebral oxygen partial pressures and CPP, and the levels of CaO₂, CjvO₂, and CERO₂ were higher in the observation group than in the control group.

These results demonstrated that administration of penehyclidine hydrochloride after undergoing cardiopulmonary resuscitation can significantly improve cerebral oxygen partial pressure, increase CPP, reduce intracranial pressure, substantially improve cerebral oxygen supply, and reduce oxygen consumption. Administration of penehyclidine can significantly delay calcium ion outflow in neuronal cytoplasm, thereby blocking L-type calcium channel expansion. This in turn results in inhibition of calcium ion transport across the cell membrane, and calcium ion release from the endoplasmic reticulum. Eventually, ATP activity is lost in neurons (13), and the occurrence of calcium overload is reduced, thereby reducing cerebral ischemia-reperfusion injury and the formation of oxygen free radicals. Administration of penehyclidine can also reduce endothelial cell damage caused by neutrophil infiltration (14). It was demonstrated that when cerebrovascular expansion occurs, oxygen supply and CPP are increased significantly (15), while the average arterial pressure does not change significantly. Therefore, intracranial pressure is relatively reduced. Comparing the levels of NSE and blood lactic acid after intervention, it was found that both the levels of NSE and blood lactic acid were lower in the observation group than in the control group. These results suggested that administration of penehyclidine after undergoing cardiopulmonary resuscitation can effectively reduce the levels of NSE and lactic acid. The underlying mechanism likely is that penehyclidine can effectively improve cell tolerance to ischemia and hypoxia, maintain lysosomal and mitochondrial activity, and reduce the levels of arachidonic acid in the body (16). Penehyclidine was shown to further reduce capillary permeability, and play a role in vasodilation and improvement of local microcirculation (17). In addition, penehyclidine has a certain degree of anti-lipid peroxidation activity (18). Therefore, administration of penehyclidine can significantly reduce the levels of NSE and lactic acid. In the analysis of oxidative stress response and inflammatory cytokines, it was found that the levels of oxidative stress markers, SOD and GSH-Px, were higher, while the levels of MDA were lower in the observation group than in the control group. Additionally, the levels of all observed inflammatory cytokines (IL-6, TNF- α , IL-1, and hs-CRP) were lower in the observation group than in the control group after intervention. These results indicated that administration of penehyclidine to patients undergoing cardiopulmonary resuscitation can significantly reduce the body's inflammatory response and oxidative stress response. Cerebral ischemia and reperfusion injury during cardiopulmonary resuscitation is related to the inflammatory responses of neuronal cells, glial cells, and vascular endothelial cells at the site of injury (18). The above biochemical markers are all associated with NF- κ B gene expression. Therefore, effective modulation of NF- κ B activity plays a key role in the treatment of cerebral resuscitation (19). Penehyclidine can effectively penetrate the blood-brain barrier, and reach effective drug concentrations in the brain. By selectively binding receptors of the M1 and M3 subtypes and N1 and N2 subtypes, it has anticholinergic effects in the central nervous system, and effectively inhibits NF- κ B protein activity (20). Comparing the areas of brain tissue edema and NIHSS scores before and after intervention, it was found that the areas of brain tissue edema were smaller and the NIHSS scores were lower in the observation group

after intervention than those before intervention, and those in the control group after intervention. These results suggested that administration of penheyclidine to patients undergoing cardiopulmonary resuscitation is of great value in reducing brain edema and improving the patient's neurological function. The mechanism is probably related to the good blood-brain barrier permeability of the drug, and its selective binding to acetylcholine receptors, thus reducing cerebral vascular endothelial permeability as well as cerebral edema, and improving neurological function (20).

In conclusion, administration of penheyclidine to patients undergoing cardiopulmonary resuscitation can effectively improve CPP, lower intracranial pressure, reduce cerebral edema and inflammation, and eventually improve neurological function.

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