EFFECTIVENESS OF HYPERBARIC OXYGEN COMBINED WITH MANNITOL IN THE TREATMENT OF ACUTE CARBON MONOXIDE POISONING AND ITS EFFECT ON THE INCIDENCE OF ADVERSE EFFECTS IN PATIENTS

Yuming Gao[1], Wei Ren[2], Haitao Cui[3], Bing Han[1], Lili Bai[4,*]

[1]Department of Emergency, Jiaozhou Central Hospital of Qingdao, Jiaozhou 266300, Shandong, China - [2]Department of Intensive Care Unit, Jiaozhou Central Hospital of Qingdao, Jiaozhou 266300, Shandong, China - [3]Department of Clinical Laboratory, Jiaozhou Central Hospital of Qingdao, Jiaozhou 266300, Shandong, China - [4]Department of Poisoning Treatment, The Fifth Medical Center of PLA General Hospital, Beijing 266300,Shandong, China

ABSTRACT

Objective: *To investigate the efficacy of hyperbaric oxygen (HBO) combined with mannitol (MT) in the treatment of acute carbon monoxide poisoning (ACOP) and its effect on the incidence of adverse reactions.*

Methods: *The clinical data of 103 ACOP patients in the emergency department of our hospital from March 2019 to March 2020 were retrospectively analyzed. The ACOP patients meeting the inclusion criteria were split into the conventional group (n=52) and the combination group (n=51) according to the order of admission. The conventional group received HBO treatment only after admission, while the combination group received MT combined with HBO to analyze the efficacy and incidence of adverse reactions in both groups by evaluating the neurological function and myocardial injury indexes at different times.*

Results: *A total of 103 subjects meeting the criteria were included in this study. In the conventional group, 52 cases were collected, 2 cases were suspended, and 50 cases were finally completed. In the combination group, 51 cases were collected, 1 case was suspended, and 50 cases were finally completed. No remarkable differences in the baseline data were observed between the two groups before treatment (P<0.05). Compared with the conventional group, the combination group achieved obviously shorter hospitalization time and awakening time (P<0.001), lower ARWMC scores at 10 days, 1 month and 3 months after treatment (P<0.00), higher MoCA scores at 1 month and 3 months after treatment (P<0.001), lower myocardial injury indexes after treatment (P<0.001), higher number of cases with complete recovery after treatment (P<0.05), lower number of cases with no recovery (P<0.05), and lower total incidence of adverse reactions (P<0.05).*

Conclusion: *The above results show that HBO combined with MT is superior to HBO alone in reducing the incidence of myocardial injury and adverse reactions in patients. Therefore, this treatment method is recommended for emergency treatment of ACOP.*

Keywords: *Hyperbaric oxygen (HBO), mannitol (MT), acute carbon monoxide poisoning (ACOP), effectiveness, incidence of adverse reactions.*

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Introduction

Acute carbon monoxide poisoning (ACOP) refers to the symptoms of local or systemic poisoning induced by inhalation of excessive carbon monoxide (CO) for a long time or a short time, which is the most common toxic gas damage in China[1-2]. Studies have found that poisoning degree of patients mainly depends on the concentration and exposure time of CO in the toxic environment. ACOP can lead to damage to multiple organs such as heart, lung and brain, in which the brain is the most seriously damaged organ because it can easily trigger delayed encephalopathy, seriously affecting the patients' quality of life and bringing a heavy burden to families[3-4]. Therefore, how to take timely and efficient rescue measures has become a research hotspot in emergency medicine. Hyperbaric oxygen

(HBO) is currently the best way to treat ACOP, but some scholars[5] have found that about 15-20% of patients suffer from delayed encephalopathy after single or multiple hyperbaric oxygen treatments, causing controversy in the medical community about this treatment method. Mannitol (MT) is a common high osmotic antihypertensive drug to reduce intracranial pressure and its efficacy in acute intracranial hypertension complicated with hemorrhagic shock has been confirmed[6]. However, there are few reports on the treatment of ACOP by HBO combined with MT, so this study aims to provide more accurate data for the clinical treatment of ACOP and provide reference for the clinic.

Materials and methods

Source of cases

The clinical data of 103 ACOP patients in the emergency department of our hospital from March 2019 to March 2020 were retrospectively analyzed. All the enrolled subjects met the inclusion criteria, were willing to participate in this study and signed informed consent. The flow diagram of this study was shown in Figure 1.

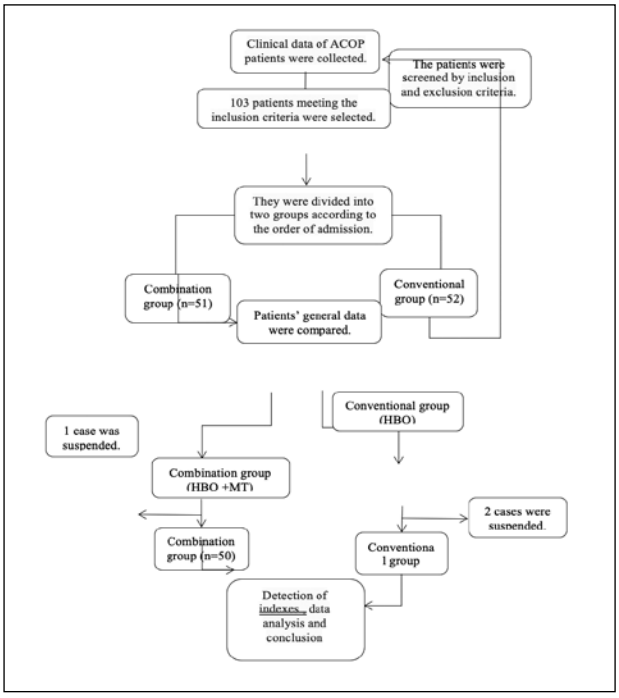

Figure 1: Flow diagram of the study.

Inclusion criteria:

• The patients met the diagnostic criteria of ACOP in Internal Medicine[7], and were confirmed by neurology and emergency departments;

• The patients had ACOP for the first time;

• The time from poisoning to treatment was no more than 2h;

• The patients met the indications of HBO therapy;

• The patient had complete baseline data.

Exclusion Criteria:

• The patients were complicated with other toxic diseases;

• The patients were complicated with cardiovascular and cerebrovascular diseases such as cerebral infarction and coronary heart disease;

• The patients had abnormal liver and kidney function;

• The patients had mild or moderate CO poisoning;

• The patients had severe cardiorespiratory dysfunction and could not receive HBO therapy.

Exit criteria:

• According to the observation and judgment of clinical professional physicians in the trial, the patients would not continue the study if serious adverse reactions occurred. The causes of adverse reactions were found out and symptomatic treatment was implemented;

• During the study, the patients could make a request for withdrawal from the trial according to their own will, and they were allowed to withdraw the study halfway.

Research methods

Pre-treatment assessment

Before treatment, the basic conditions of both groups such as blood carboxyhemoglobin and coma degree were evaluated, and the original data were recorded. If no obvious difference was found in the general data was observed between the two groups before treatment, the next step of the study could be carried out.

Treatment methods

The patients received symptomatic and supportive treatment after admission, including clearing airway, improving hypoxia, alleviating cerebral edema and maintaining electrolyte balance[8-9]. The patients in the conventional group received HBO treatment, and the oxygen chamber was the air pressurized treatment chamber produced by Guangzhou Wenda Science and Technology Co., Ltd., with the specific treatment regimen as follows. The treatment pressure was 0.14MPa, and then 30min of stable oxygen inhalation was implemented

after 15min of lifting pressure. After 5min of rest, 30min of oxygen inhalation was carried out again, and then the pressure was reduced for 15min.

The process above was carried out twice a day. The pressure was changed to 0.12MPa after the patients were awake, 1 time/day. A course of treatment included 10 days and the patients received 3 courses continuously.

In addition to HBO, MT treatment was given to the combination group. 125 ml of mannitol injection at a concentration of 20% (manufacturer: Anhui Tianyang Pharmaceutical Co., Ltd.; NMPA approval No. H34021074; specification: 250 ml: 50 g) was intravenously injected at an injection rate of 10mL/min, 2 times/day. The treatment lasted for 7 days.

Observation indexes

The clinical indexes of both groups were recorded and compared, including hospitalization time, awakening time, and incidence and mortality of delayed encephalopathy.

According to the Montreal Cognitive Assessment (MoCA)[10], the improvement of cognitive function in both groups was evaluated before treatment, and 1 month and 3 months after treatment. The scale included 11 items in 8 cognitive fields such as memory, execution function and language, with a total score of 30 points and a score ≥ 26 as normal function. A lower score represented more serious cognitive dysfunction. White matter damage scores. All patients underwent routine brain MRI examination before treatment, and 10 days, 1 month and 3 months after treatment. The white matter changes were evaluated by Age-Related White Matter Changes (ARWMC) Scale[11], with a total score of 30. A higher score suggested more serious white matter damage and wider damage range.

5 mL of fasting elbow venous blood was collected before and after treatment, and the serum was separated and stored in a refrigerator at -25 °C for further use. The levels of lactate dehydrogenase (LDH), creatine kinase (CK), creatine kinase isoenzyme (CK-MB) and troponin (cTnT) were detected by automatic biochemical analyzer (manufacturer: Nanjing Vedeng Medical Co., Ltd.; Model: BS-280).

Symptom recovery evaluation criteria:

• Complete recovery: after treatment, the patients had clear consciousness, and normal functions of lingual thinking, memory and organs without body discomfort;

• Partial recovery: the clinical symptoms and signs of poisoning were obviously improved but did not return to the normal state before poisoning, with some degree of motor and language dysfunctions, or discomfort such as dizziness and headache;

• No recovery: it referred to no improvement or even deterioration of clinical symptoms or signs of poisoning.

The incidence of adverse reactions after treatment was compared between the two groups, including oxygen intoxication, decompression disease and earache.

Statistical methods

All experimental data were statistically analyzed and processed by SPSS21.0 software, and graphed by GraphPad Prism 7 (GraphPad Software, San Diego, USA). Enumeration data were tested by X^2 and expressed by [n (%)], while measurement data were tested by t test and expressed by Mean±SD. When $P<0.05$, the differences were statistically significant.

Results

Comparison of baseline data

No remarkable differences in the baseline data such as sex ratio, average age and coma degree were observed between the two groups before treatment ($P<0.05$; Table 1).

Comparison of clinical indexes

With no obvious difference in the incidence and mortality of delayed encephalopathy between the two groups after treatment ($P>0.05$), the hospitalization time and awakening time were markedly shorter in the combination group than in the conventional group ($P<0.001$; Table 2).

Comparison of MoCA scores at different time points

The MoCA scores at 1 month and 3 months after treatment in the combination group were remarkably higher compared with the conventional group ($P<0.001$; Figure 2).

Comparison of ARWMC scores at different times points

The ARWMC scores at 10 days, 1 month and 3 months after treatment in the combination group were markedly lower compared with the conventional group ($P<0.05$; Table 3).

Items	Combination group	Conventional group	X^2/t	P
Gender			0.361	0.548
Male	24(48.00%)	27(54.00%)		
Female	26(52.00%)	23(46.00%)		
Average age (Mean±SD, years old)	38.36±4.20	38.41±4.24	0.059	0.953
BMI (Mean±SD, kg/m^2)	21.26±3.27	21.31±3.34	0.076	0.940
Time from poisoning to treatment (Mean±SD, h)	6.42±0.86	6.38±0.83	0.237	0.813
Coma time (Mean±SD, h)	10.28±1.46	10.32±1.52	0.134	0.894
Blood carboxyhemoglobin (Mean±SD, %)	28.63±3.26	28.59±3.31	0.061	0.952
Coma degree			0.178	0.673
Moderate	34(68.00%)	32(64.00%)		
Severe	16(32.00%)	18(36.00%)		
Poisoning methods				
Heating	29(58.00%)	27(54.00%)	0.162	0.687
Bathing	19(38.00%)	20(40.00%)	0.042	0.838
Suicide or other	2(4.00%)	3(6.00%)	0.211	0.646
Marital status [n(%)]				
Unmarried	4(8.00%)	6(12.00%)	0.444	0.505
Married	43(86.00%)	39(78.00%)	1.084	0.298
Divorced	3(6.00%)	5(10.00%)	0.544	0.461
Residence [n(%)]			0.041	0.840
Urban area	22(44.00%)	21(22.00%)		
Rural area	28(56.00%)	29(58.00%)		
Education level [n(%)]				
College and above	8(16.00%)	11(22.00%)	0.585	0.444
High school	24(48.00%)	24(48.00%)	0.000	1.000
Junior high school and below	18(36.00%)	15(30.00%)	0.407	0.523

Table 1: Comparison of baseline data (n=50).

Group	Hospitalization time(d)	Awakening time (h)	Incidence of delayed encephalopathy(%)	Mortality (%)
Combination group	6.37±1.73	2.95±0.47	2(4.00)	0(0.00)
Conventional group	8.35±1.36	4.26±0.52	6(12.00)	2(4.00)
t	6.362	13.215	2.174	2.041
P	< 0.001	< 0.001	0.140	0.153

Table 2: Comparison of clinical indexes (Mean±SD, n=50).

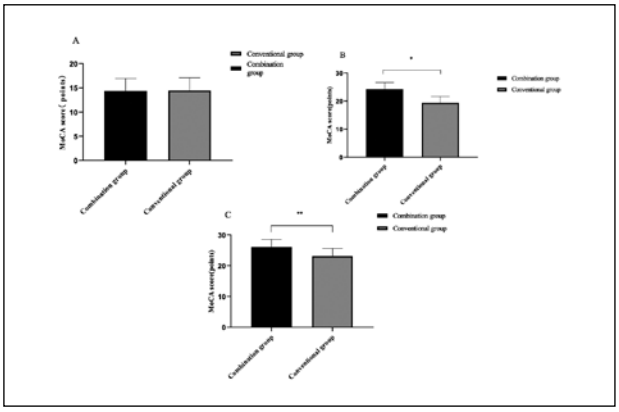

Figure 2: Comparison of MoCA scores at different time points (Mean±SD, n=50).

*Note: Figure A showed the comparison of MoCA scores before treatment. The abscissa represented the combination group and the conventional group, and the ordinate represented the MoCA score (points). The MoCA scores before treatment were (14.37±2.57) and (14.48±2.61) in the combination group and the conventional group. Figure B showed the comparison of MoCA scores at 1 month after treatment. The abscissa represented the combination group and the conventional group, and the ordinate represented the MoCA score (points). The MoCA scores at 1 month after treatment were (24.19±2.42) points and (19.35±2.34) in the combination group and the conventional group. * indicated a remarkable difference in the MoCA scores at 1 month after treatment between the two groups (t=10.167, P<0.001). Figure C showed the comparison of MoCA scores at 3 months after treatment. The abscissa represented the combination group and the conventional group, and the ordinate represented the MoCA score (points). The MoCA scores at 3 months after treatment were (26.13±2.44) points and (23.09±2.56) in the combination group and the conventional group. ** indicated an obvious difference in the MoCA scores at 3 months after treatment (t=6.078, P<0.001).*

Group	Before treatment	10 days after treatment	1 month after treatment	3 months after treatment
Combination group	18.72±3.56	15.72±2.16	11.75±2.34	8.03±1.96
Conventional group	18.81±3.48	17.31±2.08	13.27±2.26	10.74±1.86
t	0.128	3.749	3.304	7.092
P	0.899	<0.05	<0.05	<0.001

Table 3: Comparison of ARWMC scores at different times points (Mean±SD, n=50).

Comparison of myocardial injury indexes

After treatment, the myocardial injury indexes in the combination group were markedly lower compared with the conventional group (P<0.001; Table 4).

Comparison of symptom recovery

Compared with the conventional group, the number of cases with complete recovery in the combination group was obviously higher (P<0.05), while the number of cases with no recovery was lower (P<0.05), as presented in Table 5.

Group	LDH(U/L)		CK(U/L)		CK-MB(U/L)		cTnT(μg/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Combination group	495.27±43.47	142.37±23.36	1124.21±35.67	102.36±14.28	68.92±10.27	13.46±4.51	0.81±0.12	0.13±0.04
Conventional group	496.71±44.28	226.33±21.26	1125.19±36.26	173.47±15.62	69.03±10.31	23.46±3.16	0.79±0.14	0.17±0.06
t	0.164	18.796	0.136	23.759	0.053	12.840	0.767	3.922
P	0.870	< 0.001	0.892	< 0.001	0.958	< 0.001	0.445	< 0.05

Table 4: Comparison of myocardial injury indexes (Mean±SD, n=50).

Group	n	Complete recovery	Partial recovery	No recovery
Combination group	50	34(68.00)	14(28.00)	2(4.00)
Conventional group	50	26(52.00)	16(21.00)	8(16.00)
X^2		4.105	0.191	4.000
P		< 0.05	0.663	< 0.05

Table 5: Comparison of poisoning symptom recovery after treatment [n(%)].

Comparison of the incidence of adverse reactions

Table 6 presented remarkably lower total incidence of adverse reactions after treatment in the combination group than in the conventional group (P<0.05).

Group	n	Oxygen intoxication	Decompression disease	Earache	Total incidence
Combination group	50	0(0.00)	1(2.00)	2(4.00)	6.00(3/50)
Conventional group	50	3(6.00)	4(8.00)	3(6.00)	20.00(10/50)
X^2					4.332
P					0.037

Table 6: Comparison of the incidence of adverse reactions [n(%)].

Conclusion

ACOP is considered an important cause of morbidity and mortality in many countries[12]. Inhalation of a large amount of CO will cause hypoxia in tissues and organs, promote the release of a large number of oxygen free radicals, and result in lipid peroxidation of cell membranes, seriously damaging the central nervous system and cardiovascular system, and endangering the life and health of patients[13-14]. In China, ACOP is one of the common critical diseases in the emergency department in winter, and its morbidity and mortality both take up the first place in occupational hazards. Especially in the northern region with loner winter, its incidence, disability rate and mortality are rather high. The rescue principles of ACOP are to improve the hypoxia, timely correct hypoxemia and prevent the formation of cerebral thrombosis and cerebral edema[15]. High-concentration oxygen therapy after poisoning can promote hemoglobin separation and accelerate CO excretion. HBO can improve CO excretion compared with normal pure oxygen therapy, so HBO therapy after ACOP is widely accepted[16-17].

Relevant treatment guidelines[18] propose that HBO treatment should be given to ACOP patients as soon as possible when conditions permit to timely discharge CO from the body, promote patients' awakening and reduce organ damage. Although HBO is the main method to treat ACOP at present, HBO therapy alone fails to effectively control the symptoms of patients and promote the recovery of neurological function. Therefore, in order to better meet the requirements of clinical treatment of ACOP, HBO combined with drug therapy has become a hot research topic[19]. As a diuretic, MT can rapidly increase plasma osmotic pressure and reduce intracranial hypertension caused by tissue edema, and its efficacy has been confirmed in treating cerebral infarction[20-22].

The MoCA scale is often used to evaluate the recovery of cognitive function of patients. ARWMC is adopted to quantitatively evaluate the damage degree of white matter lesions, and its clinical advantages lie in that it can quickly and accurately determine the lesions and severity of white matter and basal ganglia[23-24]. Combined with MoCA scores and ARWMC scores of all patients, it was found that ACOP patients had obvious cognitive dysfunction and brain injury. After the treatment of HBO combined with MT, the therapeutic effect was markedly better compared with HBO alone, which was confirmed in the treatment of acute cerebral hemorrhage[25]. It fully shows that the above combined treatment is more effective in improving

cognitive function and brain injury of ACOP patients. The symptom recovery of both groups after treatment showed that the number of cases of complete recovery in the combination group was obviously higher compared with the conventional group ($P<0.05$), suggesting that the combined treatment was more effective. Adverse reactions such as oxygen intoxication, decompression disease and earache occurred in both groups after treatment, and disappeared after symptomatic treatment. However, the incidence of adverse reactions in the combination group was lower compared with the conventional group ($P<0.05$), indicating that the combined treatment was more safe.

This study achieved markedly better efficacy, which may be related to the younger age of the selected patients, the shorter time from poisoning to treatment, and the smaller sample size. Multi-center clinical studies with larger sample size should be carried out to explore better treatment methods for the disease in the future. In conclusion, HBO combined with MT is superior to HBO alone in protecting nerve and myocardium of patients. Therefore, this treatment method is recommended for emergency treatment of ACOP.

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Corresponding Author:
Lili Bai
Department of Poisoning Treatment, The Fifth Medical Center of PLA General Hospital, 8, Dong Da Street, Fengtai District, Beijing City, China
Email: juhuan59520951854@163.com
(China)