

‘Dexamethasone–mannitol–hyperbaric oxygen’ combination therapy is effective for patients with delayed neurological sequelae after acute carbon monoxide poisoning

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Abstract

Background: Delayed neurological sequelae after carbon monoxide poisoning (DNS) is the most common neuropsychiatric sequelae of acute carbon monoxide (CO) poisoning. At present, there is no effective method to prevent or treat DNS. This study was performed to evaluate the efficacy of the combined application of dexamethasone, mannitol and hyperbaric oxygen (HBO2) in the treatment of patients with DNS. **Methods:** A total of 312 patients with DNS were recruited and randomly assigned into the experimental group (10 mg/day dexamethasone, 100 ml/12 h mannitol + HBO2 therapy) and the control group (HBO2 only). All patients received conventional treatment. We used the Mini-Mental State Examination (MMSE) scale to assess the cognitive function, the remission rate (RR) to assess the clinical efficacy and the National Institutes of Health Stroke Scale (NIHSS) to assess the neurological function. In addition, we measured myelin basic protein (MBP) levels in the cerebrospinal fluid (CSF) to assess the extent of nerve damage. **Results:** Compared with the control group, the experimental group had significantly increased average MMSE score ($P = 0.035$) and RR ($P = 0.021$), significantly reduced average NIHSS score ($P = 0.028$) and significantly lower MBP level in CSF ($P = 0.0019$) after 4 weeks of treatment. Furthermore, compared with patients who received dexamethasone alone, patients who received dexamethasone and mannitol had higher average MMSE score ($P = 0.012$) and RR ($P = 0.038$) and lower average NIHSS score ($P = 0.022$) and MBP level in CSF ($P = 0.002$). Dexamethasone and mannitol combined with HBO2 did not significantly increase adverse effects. **Conclusion:** The combination therapy of dexamethasone–mannitol–HBO2 is better in treating DNS than HBO2 alone and HBO2 combination with dexamethasone, and it can be used as a potential new therapy in the future.

Keywords: Hyperbaric oxygen, delayed neurological sequelae after carbon monoxide poisoning, dexamethasone, mannitol, myelin basic protein

INTRODUCTION

Carbon monoxide (CO) poisoning is one of the most common causes of death from poisoning. Accidental CO poisoning occurs in approximately 15,000 people worldwide each year, accounting for approximately two-thirds of reported deaths.^{1,2} Approximately one-third of patients with coma who survive acute CO poisoning will develop delayed neurological sequelae after carbon monoxide poisoning (DNS; also called delayed encephalopathy). DNS refers to the recurrence of neuropsychiatric symptoms after an interval of apparent normality (also called ‘lucid interval’,

2–60 days, with mean duration of 22 days) following apparent recovery from acute poisoning symptoms (disorder of consciousness). The characteristic neuropsychiatric symptoms of DNS include psychiatric symptoms, short-term memory impairment, gait disturbance, seizures, cortical blindness, hallucinations, unresponsiveness, low intelligence, dementia, increased muscle tone in the limbs, incontinence and coma. The clinical outcome varies widely from complete recovery to progressive deterioration until vegetative state or death, resulting in serious economic and social burden.³⁻⁵

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The pathophysiological mechanisms of CO poisoning-induced brain damage remain unclear. Currently, DNS may be related to the tissue hypoxia induced by CO competition with haemoglobin⁶, mitochondrial oxidative stress⁷, perivascular oxidative stress caused by intravascular neutrophil activation⁸, auto-immunological attack due to the alteration in myelin basic protein (MBP)⁹, excitatory amino acid toxicity¹⁰ and oligodendrocyte regeneration failure.¹¹

To date, there is no effective way to prevent and treat DNS. Fortunately a lot of clinical neurorestorative strategies have been explored for restoring damaged nerves or sequel of neurological diseases and injuries recent years.¹²⁻¹⁴ These strategies may help to improve the chances for restoring functions or/and structures of DNS. Several studies have compared the effects of normobaric oxygen (NBO, 100% oxygen at 1 atmosphere) and hyperbaric oxygen (HBO2, 100% oxygen at 2.5–3 atmospheres) in the treatment of CO poisoning and found that both strategies can increase the dissociation rate of CO from haemoglobin by increasing the partial pressure of oxygen. However, the existing evidence cannot prove that the two strategies have different effects on the prognosis of patients with CO poisoning.¹⁵⁻²² Nevertheless, HBO2 can reverse the inflammatory response and mitochondrial dysfunction caused by CO poisoning and promote the recovery of damaged brain cells. Thus, experts in the field of hyperbaric medicine recommend HBO2 for the treatment of CO poisoning, especially patients with loss of consciousness, ischaemic heart damage, neurological deficits, severe metabolic acidosis and/or carboxyhaemoglobin (COHb) greater than 25%.⁵ If conditions permit, the above patients should be treated with HBO2 immediately. In addition, some studies have used HBO2 combined with drugs to treat DNS. Xiang *et al.* have found that the combined application of dexamethasone and HBO2 therapy is better than HBO2 therapy as a monotherapy for patients with DNS. Compared with low doses of dexamethasone, high doses of dexamethasone has better results.²³

The head computed tomography (CT) and magnetic resonance imaging (MRI) of patients with DNS often show bilateral symmetric fusion lesions in the white matter (WM) around the periventricular and semi-oval centres.²⁴ Although diffusion-weighted imaging (DWI) is often used to show the presence, severity and extent of cytotoxic oedema in early (6 h) and early (24 h), DWI signal intensity in patients with DNS symptoms 2

weeks after CO poisoning continue to increase.^{25,26} These findings suggest that neuroinflammation and oedema caused by CO poisoning may play an important role in the pathophysiology of CO poisoning-induced brain injury and the development of DNS. Therefore, this study aimed to evaluate whether the combination of 'dexamethasone–mannitol–HBO2' can further reduce the incidence and severity of DNS. In addition, some studies have suggested that MBP may be a predictor of DNS.²⁷ We also compared the MBP levels in the cerebrospinal fluid (CSF) of patients with DNS before and after treatment.

METHODS

The Medical Ethics Committee of the Sixth Medical Center of the General Hospital of the Chinese People's Liberation Army reviewed and approved the purpose and design of our work. This clinical trial was performed between May 2017 and December 2019. Patients that met the following criteria were included: 1) Patients with a clear history of CO poisoning; 2) Patients with a history of coma; 3) Patients who met the criteria of DNS; 4) Patients with Mini-Mental State Examination (MMSE) score of not more than 24; and 5) Patients or family member who provided written informed consent. The following were the exclusion criteria: 1) Patients who were allergic to dexamethasone; 2) Patients with poor blood glucose control; 3) Patients with renal insufficiency; 4) Patients with intellectual disability prior to the CO poisoning; 5) Pregnancy; 6) Patients older than 80 years; 7) Patients with bullae and pneumothorax; and 8) Patients with contraindications to HBO2. In total, 312 patients with DNS were included.

The included patients were randomly assigned into two groups in a 1:1 ratio: the experimental and control groups. We used the random number table to conduct randomisation, and the raters and patients were blinded to allocation. All patients received conventional treatments, including antibiotics and sputum suction to prevent lung infections, maintaining stable blood pressure and blood glucose, regulating water and electrolyte balance, nutrition and vitamins. The patients in the two groups were placed in the oxygen chamber with 0.16 MPa absolute pressure for 100 min/day. The patients in the experimental group were further randomly assigned into two groups in a 1:1 ratio. Half of the patients received 10 mg/day dexamethasone (E1 group). The other half received 10 mg/day dexamethasone and 100 ml/12 h mannitol intravenously (E2 group). The placebo

in the control group was given dextrose sodium chloride solution. The dosage of dexamethasone and HBO2 was according to the previous study by Xiang *et al.* with slight modifications.²³ The medication was given for 4 consecutive weeks.

Hyperbaric oxygen therapy

All the included patients in the control and experimental groups received HBO in a hyperbaric oxygen chamber (Hyperbaric Oxygen Chamber Factory, Ningbo, China) immediately after enrollment. The treatment consisted of 100% oxygen at 0.16MPa absolute pressure for 60 min (including 20 min each for compression and decompression) per treatment, once a day, 5 days per week, for 4 weeks.

Outcome assessment

The outcomes were assessed immediately after the 4-week period of treatment. The MMSE score was used to assess the cognitive function. Complete recovery (CR), partial recovery and no relief were defined according to the MMSE score. The remission rate (RR) was defined by the CR percentage. The National Institutes of Health Stroke Scale (NIHSS) was used to assess the neurological function. We also collected the CSF of patients before and after the treatment and estimated the MBP levels by enzyme-linked immunosorbent assay. The potential adverse events were recorded and analysed

Statistical analysis

We used SPSS 19.0 statistical software package

for statistical processing. Continuous data were shown as mean + standard deviation ($\bar{x}+s$). Paired t-test was used for comparison before and after treatment, and the analysis of covariance (ANCOVA) was utilised to assess the effect of the treatment modalities on the post-treatment MMSE scores, NIHSS scores and MBP level. Enumeration data were shown as frequency and percentage. Comparisons between groups were performed using χ^2 test or Fisher exact probability method. The intention-to-treat analysis was conducted, and a P-value of 0.05 was considered to be significant.

RESULTS

In total, 312 patients with DNS were included in the study. The included patients with DNS were randomly assigned into two groups, each group had 156 patients. In the experimental group, 78 patients received 10 mg/day dexamethasone and 100 ml/12 h mannitol, and the other 78 patients received 10 mg/day dexamethasone. The average CO exposure time in the experimental and control groups was (10.0 ± 2.0) h and (9.55 ± 1.2) h, respectively. The average 'lucid interval' was (15.6 ± 6.7) days and (14.9 ± 7.2) days. No significant differences were observed in other baseline data, such as age, body mass index and COHb levels between the experimental and control groups. The details of the two groups is given in Table 1. No significant difference was observed in the baseline characteristics between patients who received dexamethasone + mannitol and patients who received dexamethasone alone.

Table 1: Demographic characteristics of the included patients

Variable	Control	Experimental	t/x ²	P-value
Number	156	156	-	
Female/male	61/95	69/87	0.041	0.872
Age (years)	52.7 ± 10.6	53.1 ± 11.0	0.431	0.612
BMI (kg/mm ²)	23.7 ± 2.6	24.47 ± 3.2	0.511	0.474
Education level (years)	10.1 ± 4.2	11.07 ± 4.5	0.112	0.810
Work type (Me/Ma)	39/117	41/115	1.677	0.210
CO exposure time (h)	9.55 ± 1.2	10.0 ± 2.0	0.681	0.556
COHb levels (%)	22.7 ± 9.8	22.2 ± 10.4	0.437	0.527
Latent phase	15.6 ± 6.7	14.9 ± 7.2	0.572	0.387
Hypertension	32	35	0.910	0.343
Diabetes	27	30	0.706	0.420

MMSE score

Before the treatment, the average scores of MMSE between the experimental group and the control group were similar (experimental group: 8.40 ± 0.67 vs. control group: 8.36 ± 0.59 , $P = 0.887$). After the treatment, the average MMSE scores of the experimental and control groups were significantly increased (experimental group: after 18.75 ± 0.43 vs. before treatment 8.40 ± 0.67 , $P = 0.007$; control group: after 15.66 ± 0.41 vs. before treatment 8.36 ± 0.59 , $P = 0.002$). The ANCOVA results showed that the MMSE score of the experimental group was significantly higher than that of the control group (experimental group: 18.75 ± 0.43 vs. control group: 15.66 ± 0.41 , $P = 0.035$). Compared with patients who received dexamethasone alone, patients who received dexamethasone + mannitol had a significantly higher average MMSE score (E2 group: 18.69 ± 0.51 vs. E1 group: 15.01 ± 0.38 , $P = 0.012$) (Figures 1 and 2).

The remission rate (RR)

As shown in Table 2, the MMSE scores before treatment in both groups were <24 before treatment. After treatment, 72 patients in the experimental group and 38 patients in the control group had MMSE scores exceeding 24. These patients met the CR criteria. The RR of the experimental group was significantly higher than that of the control group (46.2% vs. 24.4%, $P = 0.021$). Compared with patients who received dexamethasone alone, patients who received dexamethasone + mannitol had significantly higher RR (56.4% vs. 35.9%, $P = 0.038$).

NIHSS score

Before the treatment, the average NIHSS scores between the experimental and the control groups

were similar (experimental group: 17.48 ± 0.29 vs. control group: 17.26 ± 0.24 , $P = 0.902$). After the treatment, the average NIHSS scores of the experimental and control groups were significantly decreased (experimental group: after 11.25 ± 0.36 vs. before treatment 17.48 ± 0.29 , $P < 0.001$; control group: after 14.62 ± 0.30 vs. before treatment 17.26 ± 0.24 , $P = 0.001$). The ANCOVA results showed that the NIHSS score of the experimental group was significantly lower than that of the control group (experimental group: 11.25 ± 0.36 vs. control group: 14.62 ± 0.30 , $P = 0.028$). Furthermore, compared with patients who received dexamethasone alone, patients who received dexamethasone + mannitol had a significantly lower average NIHSS scores (E2 group: 11.28 ± 0.28 vs. E1 group: 13.97 ± 0.33 , $P = 0.022$) (Figures 1 and 2).

MBP level

Before the treatment, no significant difference was observed in the MBP levels between the experimental and control groups (experimental group: 12.40 ± 0.31 vs. control group: 12.36 ± 0.22 , $P = 0.585$). After the treatment, MBP levels in the experimental and control groups were significantly decreased (experimental group: after 4.90 ± 0.76 vs. before treatment 12.40 ± 0.31 , $P = 0.010$; control group: after 7.62 ± 0.37 vs. before treatment 12.36 ± 0.22 , $P = 0.004$). The ANCOVA results showed that the MBP level in the experimental group was significantly lower than that in the control group (experimental group: 4.90 ± 0.76 vs. control group: 7.62 ± 0.37 , $P = 0.019$). Furthermore, compared with patients who received dexamethasone alone, patients who received dexamethasone + mannitol had a significantly lower level of MBP (E2 group: 3.75 ± 0.78 vs. E1 group: 7.23 ± 0.63 , $P = 0.002$) (Figure 3).

Table 2: RR in the two groups at baseline and end of the fourth week based on MMSE scores

Time	Group	n	0–9	0–24	25–30	RR	P-value
Baseline	Control	156	114	42	0	-	-
	E1	78	57	21	0	-	-
	E2	78	59	19	0	-	-
Fourth week	Control	156	100	18	38	24.4%	0.021 ^a
	E1	78	30	20	28	35.9%	0.038 ^b
	E2	78	4	30	44	56.4%	

Notes: a) P-value of the control vs. experimental group on RR; b) P-value of E1 vs. E2 on RR; E1, patients who received 10 mg/day dexamethasone + 125 ml per 12 h mannitol; E2, patients who received 10 mg/day dexamethasone. Abbreviations: MMSE, Mini-Mental State Examination; RR, remission rate.

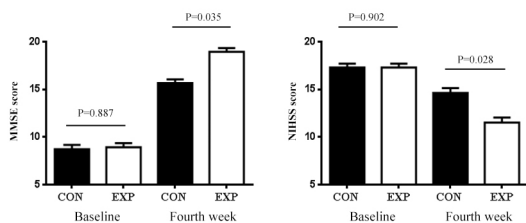


Figure 1. MMSE and NIHSS scores in the experimental and control groups.

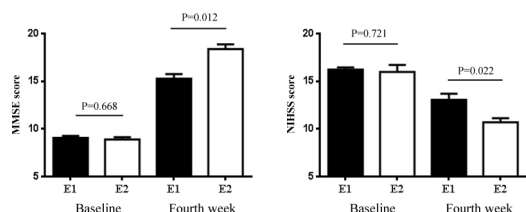


Figure 2. MMSE and NIHSS scores in E1 (10 mg/day dexamethasone) and E2 (100 ml per 12 h mannitol and 10 mg/day dexamethasone) groups.

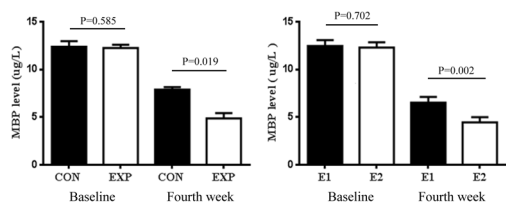


Figure 3. Level of MBP in CSF of patients with DNS.

Adverse events

During the whole course of treatment, no serious adverse events were observed in the two groups. No significant increase in blood glucose or renal impairment was observed. In the experimental group, 1 case of mild nausea, 1 case of bloating, 1 case of phlebitis and 1 case of dizziness were noted. In the control group, 1 patient had mild nausea, 3 patients had mild headache, and 2 patients had loss of appetite. All patients with adverse events recovered by themselves and did not require special treatment.

DISCUSSION

Since the use of HBO2 in the treatment of CO poisoning in 1960, the effects, timing and sessions of HBO2 therapy have been controversial due to methodological limitations. Six prospective clinical trials have compared the clinical efficacy of HBO2 and NBO in the treatment of acute CO poisoning, four of which have found better clinical

outcomes for HBO2, whereas two have no positive effect. To date, most experts in the field have advocated that HBO2 can be used to treat severe CO poisoning to limit delayed and permanent neurological sequelae.^{15,16,22,28-32} Once DNS occurs, symptomatic and supportive treatments are often used.³³ HBO2 is widely used in China to treat DNS on the basis that it increases blood oxygen content in brain tissues, exerts anti-inflammatory and antioxidant effects, and promotes stem cell differentiation and proliferation and recovery of damaged nerve cells.³⁴

Hypoxic-ischemic, excitotoxicity, acidosis, ion imbalance and depolarisation, oxidative stress, nitrification stress, inflammation, apoptosis and oligodendrocyte regeneration failure may be involved in CO poisoning-induced brain damage and DNS. However, none of the above mechanisms can fully explain its pathogenesis.^{6-11,35} Increasing evidence suggests that delayed neuropathology after CO poisoning is immune-mediated.⁹ CO poisoning can activate platelets by replacing nitric oxide from platelet blood proteins. Free nitric oxide reacts with superoxide to form peroxynitrite, which further increases platelet activation. Activated platelets can stimulate neutrophil degranulation and release myeloperoxidase (MPO), thereby activating neutrophil activation, adhesion and degranulation, further enhancing immune inflammatory effects. Proteases in neutrophils can oxidise endothelial xanthine dehydrogenase to xanthine oxidase to produce reactive oxygen species (ROS). MPO and ROS catalyse lipid metabolism, and oxidation forms an adduct with MBP (the main component of the central nervous system, accounting for approximately 30% of myelin proteins), activating lymphocyte responses and microglial activation, inducing autoimmune cascades and further degrading MBP in the brain. When MBP is degraded and released into the CSF and blood, it can further cause an autoimmune response, attack the normal brain MBP and induce progressive demyelination, leading to DNS.^{9,36-39} MBP in CSF can be used as a predictor of DNS.^{27,40-42} Therefore, blocking the immune inflammatory response may be an effective means to prevent the occurrence and development of DNS. Glucocorticoids have powerful anti-immune effects. Li *et al.* found that dexamethasone may reduce the inflammatory response by protecting the myelin sheath from the inflammatory response and also reduce the oedema and permeability of hypoxic-ischaemic brain tissue and neuronal damage.⁴³ Atalay *et al.* reported that dexamethasone may treat CO

poisoning rats by intervening in brain tissue lipid peroxidation.⁴⁴ Xiang *et al.* conducted a series of studies on the role and mechanism of dexamethasone in DNS treatment at the animal and clinical levels. They found that dexamethasone treatment could inhibit neutrophil activation and inflammatory response-mediated nerve damage by inhibiting MPO expression and significantly reduced the escape latency of rats and MBP expression levels in serum and hippocampus. In addition, they recruited 120 patients with DNS to evaluate the neurocognitive function, RR and MBP expression in the CSF of dexamethasone combined with HBO2 therapy. They found that after 4 weeks of treatment, the experimental group had a significantly higher RR and average MMSE score and a significantly lower average NIHSS score compared with the control group. Meanwhile, a trend toward better improvement with dexamethasone 10 mg/day was observed, and the MBP level in the CSF of patients was significantly lower in the experimental group than in the control group. The addition of dexamethasone did not significantly increase the incidence of adverse events.^{23,45} Based on our experience in the clinical treatment of DNS in recent years and Xiang *et al.*'s study, we designed this study and found that HBO2 therapy as monotherapy and the combined application of 10 mg/day dexamethasone and HBO2 therapy could significantly improve the MMSE score and reduce the NIHSS score and MBP level. In addition, the RR is high in patients with DNS. These results indicate that the combined application of dexamethasone and HBO2 therapy could indeed yield better efficacy for patients with DNS and should be regarded as a potential new therapy.

DWI can objectively and quantitatively indicate the degree of diffusion of water molecules in tissues. It is more sensitive than conventional MRI and can demonstrate cytotoxic oedema in damaged WM earlier. Cytotoxic oedema in acute ischemic lesions is characterised as high signal on DWI and low ADC value.⁴⁶ DWI examination in patients with acute or subacute stage of CO poisoning showed decreased ADC values and increased DWI signals at bilateral frontal and parietal WM at 12 and 48 h after CO poisoning.^{47,48} DWI studies on the subacute and chronic phases of CO poisoning found that the WM areas with high DWI signals and low ADC value during the acute phase persisted in the subacute and chronic phases.⁴⁹ Patients with DNS can have high DWI signals and low ADC values for 1–2 months.^{24,50} Therefore, the DWI

performance of patients with CO poisoning and cerebral infarction is different (ADC values are low at 3–5 days and return to normal within 1–4 weeks after stroke). This result suggests that WM damage in patients with CO poisoning cannot be simply explained by local ischaemia, but patients with DNS may develop progressive demyelination with cytotoxic oedema. Drugs currently available for controlling oedema include mannitol, hypertonic saline and corticosteroids. Amongst them, mannitol has the longest clinical application and the widest range. As a hypertonic drug, the main mechanisms of mannitol dehydration are osmosis and haemodynamics. Mannitol does not cross the cell membrane or the intact blood–brain barrier; thus, it increases intravascular tension, thereby establishing a concentration gradient across the blood–brain barrier, forcing water to move from the oedema brain tissue into the blood vessels. The haemodynamic effects of mannitol are thought to be mediated by a decrease in blood viscosity, which results in an increase in cerebral blood flow and a subsequent decrease in cerebral blood volume due to passive vasoconstriction.⁵¹ Although mannitol has a poor effect on cellular oedema, it also has the effects of scavenging free radicals, inhibiting apoptosis and regulating cerebral perfusion pressure (increasing cerebral perfusion pressure leading to self-regulating vasoconstriction and subsequent reduction of cerebral blood volume).⁵² We found that compared with the HBO2 alone and HBO2 combination with dexamethasone groups, the ‘10 mg/day dexamethasone + 100 ml/12 h mannitol + HBO2’ combination therapy for patients with DNS could further improve the MMSE score and RR, reduce the NIHSS score and MBP levels and did not significantly increase the incidence of adverse events. Therefore, these results indicate that the combined application of ‘dexamethasone + mannitol + HBO2’ may be a potentially effective treatment for patients with complications of DNS.

In conclusion, our study found that ‘dexamethasone + mannitol + HBO2’ combination therapy is better than HBO2 as a monotherapy and dexamethasone + HBO2 therapy in patients with DNS. It is a potentially effective strategy for the prevention and treatment of DNS. However, some limitations exist in our study. 1) We did not conduct the sample size calculation. 2) We only assessed the efficacy of dexamethasone, mannitol and HBO2 therapy in the acute phase treatment of DNS. Thus, future studies are needed to assess its long-term efficacy. 3) We only randomised the patients into two groups

(control and experimental) and then splitting the experimental group because our study followed the study by Xiang *et al.*²³ It would have been better to randomise the recruited patients into three groups (control, E1 and E2) right from the start. Thus, a large sample, multi-centre, randomised controlled study is needed to further validate our findings.

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DISCLOSURE

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Conflicts of interest: None

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