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Targeting optimal time for hyperbaric oxygen therapy following carbon monoxide poisoning for prevention of delayed neuropsychiatric sequelae: A retrospective study

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ABSTRACT

Objectives: Delayed neuropsychiatric sequelae (DNS) are serious complications of carbon monoxide poisoning; neuropsychiatric disorders can occur within a few days of recovery from acute poisoning. Hyperbaric oxygen therapy (HBOT) has been the main treatment of carbon monoxide (CO) poisoning and was recommended as the treatment choice for CO poisoning by the American Undersea and Hyperbaric Medical Society and the Tenth European Consensus Conference on Hyperbaric Medicine of the European Underwater and Baromedical Society. However, the optimal timing for commencing HBOT in patients with CO poisoning remains unknown. We therefore conducted a retrospective study in an attempt to target the optimal time of HBOT for DNS prevention.
Methods: A retrospective review of patient files/medical records was conducted on all patients with CO poisoning admitted to the Emergency Department of Linkou Chang-Gung Memorial Hospital, Taiwan between January 1, 2009 and December 31, 2015. A total of 279 patients who received HBOT were eligible for further DNS detection. DNS was defined as the presence of one of the following neurological, cognitive, or psychological sequelae that were documented in the medical record during hospital stay or outpatient clinic follow-up for at least 6 months. A multivariable logistic regression analysis was employed to identify potential determinants of DNS after receiving HBOT for CO poisoning. A receiver operating characteristic (ROC) curve was used to analyse the influence of duration from CO exposure to HBOT on DNS development.
Results: A Glasgow coma score of < 9 (odds ratio [OR], 3.20; 95% confidence interval [CI], 1.19–8.60) and a longer duration from CO exposure to HBOT (OR, 1.06; 95% CI, 1.03–1.09) were associated with a higher risk of DNS. By contrast, the presence of multiple victims from the same incident was associated with a lower risk of DNS. The ROC curve for the duration between CO exposure and HBOT in predicting DNS development demonstrated an area under the curve of 0.638 (95% CI, 0.575–0.698). The optimal cut-off point according to the Youden index was 22.5 h, with a sensitivity of 41.7% and a specificity of 85.9%. We also stratified the duration from CO exposure to HBOT into 5 intervals (< 6 h, 6–11 h, 12–23 h, 24–47 h and ≥ 48 h) and revealed a trend of increasing DNS risk with time.
Conclusions: We identified several potential predictors of DNS in patients with CO poisoning who received HBOT. Multivariable logistic regressions further revealed that longer duration from CO exposure to HBOT, loss of consciousness, and the presence of multiple victims were independent predictors of DNS development. HBOT should be performed as early as possible and preferably within 22.5 h after CO poisoning.

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1. Introduction

Carbon monoxide poisoning is one of the major causes of unintentional and intentional morbidity and mortality in modern society [1]. In addition to poisoning-related mortality observed in acute stage, delayed neuropsychiatric sequelae (DNS) can occur in the recovery stage, which requires more attention. Acute neurotoxicity manifesting altered mental status that develops after CO poisoning is primarily caused by CO binding to haemoglobin to induce brain hypoxemia [2–5], but the exact pathophysiology of DNS remains unclear. Prior studies have demonstrated that increased reactive oxygen species (ROS), depletion of antioxidant defence systems, enhancement of lipid peroxidation, binding to cytochrome *aa*3, and disruption of intracellular oxygen utilisation of brain are related to CO-mediated delayed neuropathology [6,7]. Furthermore, studies have indicated that oxidation status, antioxidant depletion, and lipid peroxidation of the cerebral cortex, globus pallidus, and hippocampus are time-dependently associated with the risk of CO poisoning [7–9].

Possible methods for the treatment and prevention of DNS after CO poisoning other than hyperbaric oxygen therapy (HBOT) have been investigated, which include hypothermia [10], neuroprotective agents such as N-butylphalide and resveratrol, oxidative stress inhibitors, agents for the preservation of mitochondrial function such as methylene blue [11], and edaravone for the inhibition of apoptosis and oxidative stress [12]. However, these studies are either limited to animal experiments or simply case reports, both of which are far from larger scale human applications. HBOT therefore remains the main treatment of choice for CO poisoning worldwide [13–15]. The half-life of carboxyhaemoglobin (COHb) is rapidly shortened as the fraction of inspired oxygen increases, and is approximately 5 h at room atmosphere, 90 min with pure oxygen at a pressure of 1 atm absolute (ATA), and 20 min with pure oxygen at 2 ATA [16]. The efficacy of HBOT has been studied in many clinical trials, which nevertheless yielded conflicting results. [5,16–24].

The inconsistent results of HBOT may be related to between-study variation in the severity of CO poisoning, intervention time and treatment delay, as well as the evaluation criteria of DNS [21]. Heterogeneous conditions between clinical scenarios render studies of HBOT and normobaric oxygen (NBO) therapy difficult to interpret [19]. For example, a study revealed that only patients who had an initial loss of consciousness benefited from HBOT for DNS prevention [16]. Moreover, patients with coma experienced significantly more benefits from receiving one session of HBOT than two sessions of therapy [16,21]. By contrast, a prospective, randomised study of patients with mild to moderate CO poisoning who presented to the emergency department (ED) within 6 h concluded that HBOT (mean 2 ± 0.2 h) could decrease the incidence of DNS after CO poisoning [18]. Weaver et al. also concluded that three HBOT sessions within a 24-h period reduced the risk of cognitive sequelae in a double-blind randomised trial [2,5]. Although most studies have advocated HBOT as soon as possible after CO poisoning, studies on HBOT delay have been inconclusive [25].

Research has increasingly focused on the effect of oxidative and antioxidative inducement of HBOT in patients with CO poisoning. CO poisoning related oxidative stress is not instantaneous, and HBOT alters the balance between the oxidative and antioxidative status of patients [7,8,11,26–28]. We herein conducted a retrospective study to identify the possible time-dependent effects of HBOT on DNS prevention after CO poisoning and to target the optimal time for HBOT after CO exposure.

2. Methods

2.1. Ethics

The study protocol was approved by the Chang-Gung Medical Foundation Institutional Review Board, and permission was granted (104-7628C) by the Medical Ethics Committee of Chang-Gung Memorial Hospital.

3. Study design, setting, population, and selection of participants

A retrospective review of medical records was conducted on all patients with CO poisoning admitted to the ED of Linkou Chang-Gung Memorial Hospital (CGMH), a 3700-bed tertiary medical center from January 1, 2009 to December 31, 2015. COHb levels were measured using an arterial blood gas analysis with a CO-oximeter. All enrolled patients met both the following criteria: 1. COHb level measured at the first medical institution was > 5% in non-smokers or > 10% in smokers; and 2. a witnessed CO exposure scenario (e.g., burning charcoal, exposure to machine exhaust in a confined space, incomplete combustion of water heater or incorrect furnace use).

4. Data collection and definition of variables

For all patients with confirmed CO poisoning, data on the following baseline characteristics were abstracted from the medical records: age, sex, past psychiatric history, referral institution, voluntary or accidental exposure, CO exposure source, initial vital signs at the ED, Taiwan triage and acuity score [29], concomitant use of tranquillisers, transient loss of consciousness, duration of loss of consciousness, time elapsed from CO exposure to ED admission, evidence of myocardial injury (defined as electrocardiographic signs of ischemia, arrhythmia, or cardiac enzyme elevation), electrocardiogram; modified Poisoning severity score (PSS) [30], brain computed tomography (CT) scan, treatment modality (HBOT at 2.5 ATA for 90 min with air/break 25/5 min or 100% NBO through a 'non-rebreathing' facemask [NRM]), session number of HBOT, time elapsed from CO exposure to HBOT, and length of admission and intensive care unit stay. Data on blood tests, obtained at the time of admission and during the patients' hospital stay, were also collected and included a complete blood cell count, artery blood gas analysis, COHb level, troponin I level, creatine phosphokinase level, and serum alcohol level. Urine samples were screened at the ED for benzodiazepines and illicit drugs.

All patients with CO poisoning received supplementary 100% oxygen through NRM upon arrival at the ED. In our hospital, patients with CO poisoning are considered for HBOT after consultation with HBOT physician following the guidelines of HBOT for CO poisoning of American Undersea and Hyperbaric Medical Society (Table 1). DNS were defined as the recurrence of original symptoms or the development of new symptoms such as difficulty concentrating, lethargy, emotional lability, mutism, amnestic syndromes, dementia, cognitive impairment, Parkinsonism, apraxia, unsteady gait, urinary

Table 1
Hyperbaric oxygen therapy (HBOT) indications for CO poisoning and relevant treatment protocol in Chang-Gang Memorial Hospital (CGMH).

I. HBOT indication for CO poisoning
  a. Loss of consciousness
  b. Ischemic cardiac changes
  c. Neurological deficits
  d. Significant metabolic acidosis
  e. Carboxyhemoglobin ≧25%
  f. Pregnant women
II. HBOT treatment protocol in CGMH
  a. Patients receive treatment at 2.5 atm absolute for 90 min with 25/5 mins air-break
  b. Frequency: once daily
  c. Total number of sessions suggested by hyperbaric oxygen physician: ≧3 times
  d. Oxygen supplement route in HBOT chamber: face mask

Adopted from "Practice recommendations in the diagnosis, management, and prevention of carbon monoxide poisoning," by Neil B. Hampson, Claude A. Piantadosi, Stephen R. Thom, and Lindell K. Weaver Am. J Respir Crit Care Med, 2012;186:1095–1101, Copyright 2012 by the American Thoracic Society.

Table 2
Previously reported signs and symptoms of delayed neuropsychiatric sequelae.

Neurological sequelae	Cognitive and psychological sequelae
Parkinson-like syndromes	Concentration deficit
Gait and motor disturbances	Memory loss
Bradykinesia	Cognitive impairment
Intention tremor	Dementia
Myoclonus	Personality changes
Dyspraxia	Anxiety
Dysphasia	Extreme emotional lability
Ataxia	Psychosis
Postural instability	Depression
Vertigo	Mania
Cortical blindness	Insomnia
Hearing loss, tinnitus	
Chorea	
EEG abnormalities	
Epilepsy	
Peripheral neuropathies	
Recurrent headache	
Fecal/urinary incontinence	

Adopted from "Delayed neuropsychological sequelae after carbon monoxide poisoning: predictive risk factors in the emergency department. A retrospective study" by Giuseppe Pepe, Matteo Castelli, Peiman Nazerian, Simone Vanni, Massimo Del Panta, Francesco Gambassi, et al., Scand J Trauma Resusc Emerg Med, 2011;19:16.

incontinence, etc. within 2–42 days after CO poisoning (Table 2) [31]. All poisoned patients were invited to the follow-up visits from hospital discharge in outpatient clinics. A comprehensive neurological exam and mental status examination were performed by a neurologist or a psychiatrist during the follow-up visits. The follow-up duration to observe the development of DNS was at least 6 months.

After the development of DNS, EEG and/or brain image studies including CT scan and magnetic resonance imaging were arranged; further HBOT sessions were also considered.

5. Statistical analysis

We compared the baseline characteristics between patients who received HBOT and those who did not by employing the Fisher's exact test for categorical variables or use independent sample *t*-tests for continuous variables to investigate the factors associated with DNS development. Variables with a P value of < 0.2 in univariate analyses were entered into a multivariable logistic regression model using stepwise selection. The influence of the duration between CO exposure and HBOT on DNS development was assessed using a receiver operating characteristic (ROC) curve. Finally, the correlation between the time elapsed after CO exposure to HBOT and the risk of DNS was examined using a Cochran–Armitage chi-square analysis. All data analyses were conducted using MedCalc software version 13.1.2 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2014).

6. Results

Of 760 patients with CO poisoning admitted to the ED from 2009 to 2015, 452 received follow-up for at least 6 months and were thus eligible for further detection of DNS. Among them, 279 patients received HBOT. Table 3 lists the baseline characteristics of patients who received HBOT and those who did not. Patients who received HBOT differed from those who did not receive HBOT by the following characteristics:more frequent registration in the night, higher severity score on the triage scale, more likely to be transferred from an outside institution, longer duration from CO exposure to ED admission, higher prevalence of loss of consciousness, higher COHb values measured at the first institution, higher proportion of myocardial injury, greater severity of modified PSS of CO poisoning [30], higher incidence of complications, more likely to be hospitalised, and higher incidence of DNS ($P < .05$). Moreover, in the group that did not receive HBOT, 9.2% (16/173) were recommended to receive HBOT after an HBOT physician consultation, yet the patients refused the suggestion.

Table 4 displays the baseline characteristics of patients with and without DNS for those who received HBOT. Patients who developed DNS tended to have the following characteristics: more likely to be male, higher prevalence of psychiatric history, more frequently admitted at daytime, lower Glasgow Coma Score (GCS), higher severity score on the triage scale, higher rate of suicide attempt history, more likelihood of CO poisoning caused by charcoal burning, less likely to have multiple victims, longer duration from CO exposure to ED

Table 3
Demographic and clinical data of CO poisoned patients with and without receiving hyperbaric oxygen therapy (HBOT).

Variables	HBOT (n = 279)	Non-HBOT (n = 173)	P value
Male gender	130 (46.6)	92 (53.2)	0.177
Age, year	34.2 ± 17.0	33.3 ± 19.3	0.607
Psychiatric history	42 (15.1)	38 (22.0)	0.076
Emergency department (ED) visit time			0.015
08:01–16:00	60 (21.5)	40 (23.1)	
16:01–24:00	114 (40.9)	90 (52.0)	
00:01–08:00	105 (37.6)	43 (24.9)	
Glasgow Coma Scale (GCS)	13.5 ± 3.1	13.3 ± 3.5	0.375
GCS < 9	27 (9.7)	21 (12.1)	0.434
Triage scale			0.022
1 (life-threatening)	31 (11.1)	29 (16.8)	
2 (emergent)	194 (69.5)	96 (55.5)	
3 (urgent)	50 (17.9)	44 (25.4)	
4 (less urgent) and 5 (not urgent)	4 (1.4)	4 (2.3)	
Transferred from outside institution	168 (60.2)	51 (29.5)	< 0.001
Attempt to suicide	108 (38.7)	69 (39.9)	0.843
Source of CO poisoning			0.067
Charcoal burning	117 (41.9)	66 (38.2)	
Water heater incomplete combustion or incorrect Use of furnace	149 (53.4)	89 (51.4)	
Others	13 (4.7)	18 (10.4)	
Presence of multiple victims	134 (48.0)	78 (45.1)	0.562
Time from CO exposure to ED visit, hour	9.4 ± 15.0	6.0 ± 9.6	0.011
Transient loss of consciousness	203 (72.8)	75 (43.4)	< 0.001
Duration of loss of consciousness			< 0.001
< 6 h.	150 (53.8)	60 (34.7)	
6–12 h.	26 (9.3)	2 (1.2)	
13–24 h.	14 (5.0)	6 (3.5)	
> 24 h.	13 (4.7)	3 (1.7)	
> 48 h	0 (0.0)	4 (2.3)	
No loss of consciousness	76 (27.2)	98 (56.6)	
COHb, % (measured at first medical institution)	27.5 ± 14.3	20.9 ± 15.5	< 0.001
Evidence of myocardial injury			0.002
No	175 (62.7)	114 (65.9)	
Yes	47 (16.8)	11 (6.4)	
Unknown	57 (20.4)	48 (27.7)	
Brain CT at first medical institution	86 (30.8)	39 (22.5)	0.066
Modified Poisoning Severity Score			< 0.001
Minor	76 (27.2)	100 (57.8)	
Moderate	164 (58.8)	49 (28.3)	
Severe	39 (14.0)	24 (13.9)	
Presence of any complications	70 (25.1)	27 (15.6)	0.018
Disposition of ED			< 0.001
Discharged on the same day of ED visit	45 (16.1)	69 (39.9)	
Stay overnight in the ED	65 (23.3)	68 (39.3)	
Admission	159 (57.0)	23 (13.3)	
Intensive care unit	10 (3.6)	13 (7.5)	
HBO physician consultation	279 (100)	77 (44.5)	< 0.001
HBOT suggested by HBO physician	279 (100)	16 (9.2)	< 0.001
Persistent neurological sequelae	2 (0.7)	0 (0.0)	0.526
Delayed neuropsychiatric sequelae	48 (17.2)	13 (7.5)	0.004

Continuous data were expressed as mean ± standard deviation; whereas categorical data were presented as frequency (proportion).

Table 4
Demographic and clinical data of CO poisoned patients with and without delayed neuropsychiatric sequelae (DNS) among those who received hyperbaric oxygen therapy (HBOT).

Variables	DNS (n = 48)	Non-DNS (n = 231)	P value
Male gender	29 (60.4)	100 (43.3)	0.022
Age, year	38.4 ± 16.1	33.3 ± 17.1	0.060
Psychiatric history	13 (27.1)	30 (13.0)	0.026
Emergency department (ED) visit time			< 0.001
08:01–16:00	20 (41.7)	39 (16.9)	
16:01–24:00	20 (41.7)	95 (41.1)	
00:01–08:00	8 (16.7)	97 (42.0)	
Glasgow Coma Scale (GCS)	11.9 ± 4.2	13.9 ± 2.6	< 0.001
GCS < 9	11 (22.9)	16 (6.9)	0.002
Triage scale			0.029
1 (life-threatening)	10 (20.8)	21 (9.1)	
2 (emergent)	28 (58.3)	166 (71.9)	
3 (urgent)	8 (16.7)	42 (18.2)	
4 (less urgent) and 5 (not urgent)	2 (4.2)	2 (0.9)	
Transferred from outside institution	32 (66.7)	137 (59.3)	0.418
Attempt to suicide	33 (68.8)	76 (32.9)	< 0.001
Source of CO poisoning			< 0.001
Charcoal burning	36 (75.0)	82 (35.5)	
Water heater incomplete combustion or incorrect Use of furnace	10 (20.8)	138 (59.7)	
Others	2 (4.2)	11 (4.8)	
Presence of multiple victims	7 (14.6)	127 (55.0)	< 0.001
Time from CO exposure to ED visit, hour	21.6 ± 29.1	7.2 ± 8.8	< 0.001
Transient loss of consciousness	43 (89.6)	160 (69.3)	0.004
Duration of loss of consciousness			< 0.001
< 6 h.	21 (43.8)	128 (55.4)	
6–12 h.	5 (10.4)	22 (9.5)	
13–24 h.	9 (18.8)	5 (2.2)	
> 24 h.	8 (16.7)	5 (2.2)	
> 48 h	0 (0.0)	0 (0.0)	
No loss of consciousness	5 (10.4)	71 (30.7)	
COHb, % (measured at first medical institution)	23.6 ± 17.2	28.2 ± 13.7	0.047
Evidence of myocardial injury			0.008
No	22 (45.8)	153 (66.2)	
Yes	15 (31.3)	32 (13.9)	
Unknown	11 (22.9)	46 (19.9)	
Brain CT at first medical institution	28 (58.3)	58 (25.1)	< 0.001
Modified Poisoning Severity Score			0.001
Minor	5 (10.4)	71 (30.7)	
Moderate	29 (60.4)	134 (58.0)	
Severe	14 (29.2)	26 (11.3)	
Presence of any complications	21 (43.8)	50 (21.6)	0.003
Interval from CO exposure to HBOT, hour	37.9 ± 47.0	16.9 ± 14.4	< 0.001
Number of HBOT sessions	5.5 ± 5.4	2.6 ± 1.8	< 0.001
Disposition of ED			0.077
Discharged on the same day of ED visit	4 (8.3)	41 (17.7)	
Stay overnight in the ED	9 (18.8)	56 (24.2)	
Admission	31 (64.6)	128 (55.4)	
Intensive care unit	4 (8.3)	6 (2.6)	

Continuous data were expressed as mean ± standard deviation; whereas categorical data were presented as frequency (proportion).

admission, higher prevalence of loss of consciousness, higher proportion of myocardial injury, positive findings of brain CT, higher incidence of complications, and longer duration from CO exposure to HBOT (P < .05).

Table 5 presents the risk factors for DNS development in 279 patients who received HBOT. Those variables with a P value of < 0.2 in the univariate analyses (Table 4) were then included in the multivariate model using stepwise selection. The results demonstrated that a GCS of < 9 (odds ratio [OR], 3.20; 95% confidence interval [CI], 1.19–8.60) and a longer duration from CO exposure to HBOT (OR, 1.06; 95% CI, 1.03–1.09) were associated with a higher risk of DNS development. Additionally, the presence of multiple victims was correlated to a lower risk of DNS development (OR, 0.24; 95% CI, 0.09–0.61).

Table 5
Factors associated with delayed neuropsychiatric sequelae development for patients who received hyperbaric oxygen therapy (HBOT).

Variables	Odds ratio (95% CI)	P value
GCS < 9	3.20 (1.19–8.60)	0.021
Multiple victims	0.24 (0.09–0.61)	0.003
Duration from exposure to HBOT (hour)	1.06 (1.03–1.09)	< 0.001

Variables with a P value < .2 in the univariate analyses were introduced into the multivariable model using stepwise selection; CI, confidence interval.

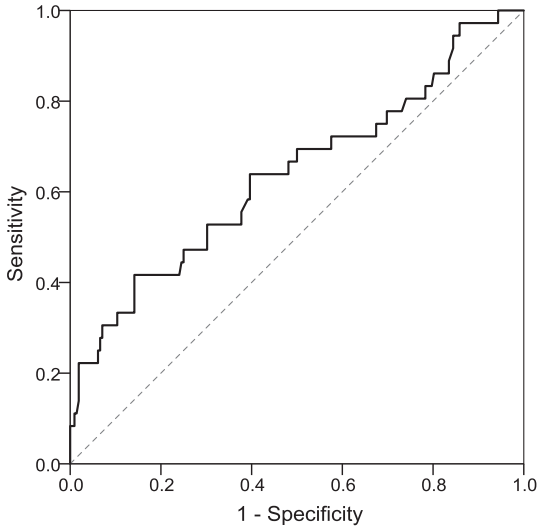

Fig. 1. The receiver operating characteristic (ROC) curve for the duration from CO exposure to hyperbaric oxygen therapy (HBOT) that predicted the development of delayed neuropsychiatric sequelae in patients who received HBOT. The area under the ROC curve is 0.638 (95% CI, 0.575–0.698). The best cutoff point is 22.5 h with a sensitivity of 41.7% and a specificity of 85.9%.

Fig. 1 illustrates the ROC curve for the duration from CO exposure to HBOT that determines DNS development. The area under the ROC curve is 0.638 (95% CI, 0.575–0.698), which is unsatisfactory but acceptable. The optimal cut-off point according to the Youden index is 22.5 h, with a sensitivity of 41.7% and a specificity of 85.9%. We further split the samples into five groups according to the duration from CO exposure to HBOT. A longer duration is correlated with an increased risk of DNS (P < .001; Fig. 2).

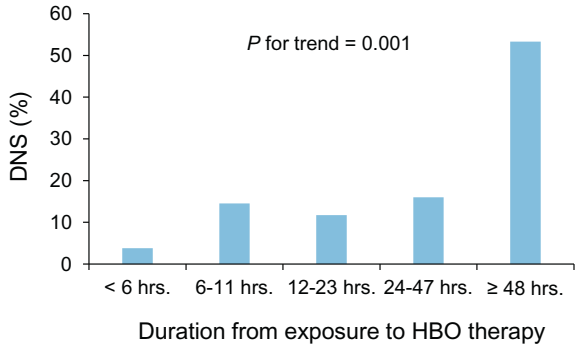

Fig. 2. The proportion of patients with delayed neuropsychiatric sequelae (DNS) stratified by the duration from CO exposure to hyperbaric oxygen (HBO) therapy.

7. Discussion

Our study demonstrated that DNS development was significantly increased in the group of patients with longer durations from CO exposure to HBOT and with a loss of consciousness or coma upon presenting to the first institution. By contrast, DNS development was inversely associated with the presence of multiple victims of CO poisoning. Furthermore, an acceptable timing for HBOT was within 22.5 h after CO poisoning, and there was no benefit on the prevention of DNS if HBOT was administered > 48 h after CO poisoning.

Treatment of acute CO poisoning consists of CO offloading and the promotion of CO dissociation from haemoglobin through oxygen administration in the acute stage. HBOT causes CO off-gassing faster than NBO. Both interventions, especially HBOT, increase the rate of CO–haemoglobin dissociation, oxygen transport into tissues, and hypoxia resolution [4,20]. Adverse events regarding the therapeutic protocols of HBOT were rare (0.68%) in a large-scale study and might include otic or sinus barotrauma, confinement anxiety, hypoglycaemia, oxygen toxicity, pneumothorax, seizure, and shortness of breath. Barotrauma and confinement anxiety were the most frequently reported events; whereas severe medical events such as oxygen toxicity and pneumothorax were extremely uncommon [32]. Based on the safety of HBOT and the uncertain treatment strategies for DNS prevention after CO poisoning, HBOT remains vital in the 21st century. HBOT of patients that are drowsy or present with initial loss of consciousness or coma at the ED following acute CO poisoning is generally recommended [16,17,21,25].

The study of Dacusse et al., reported that HBOT must be administered as soon as possible for CO poisoning [17]. Thom et al., concluded that successful HBOT may require administration of the therapy within 6 h of CO poisoning, which was associated with a significant reduction in the incidence of DNS [18]. A randomised controlled trial conducted by Raphael et al., enrolled patients who had been poisoned within 12 h before admission to the hospital and received one session of HBOT. Notably, HBOT only benefited those who lost consciousness after CO poisoning [16]. In the randomised control trial conducted by Weaver et al., HBOT was administered at a mean time of 13 ± 41 h after CO exposure and was found to be effective against the development of DNS [5,33]. However, under real circumstances, the initial treatment time for HBOT is frequently delayed because the therapy depends on the availability of the HBO chamber, man power of HBOT physician and technicians, and the referral time. These factors may lead to the failure of HBOT being performed in the previously mentioned timeframe. Therefore, it is crucial to identify the optimal time for HBOT among patients with CO poisoning in a real-world clinical setting.

The pathophysiology of CO-related DNS remains unclear. Most researchers consider demyelination and the neurons destruction of cerebral white matter and the globus pallidus induced by CO poisoning to be the main pathological features of DNS. Inflammation caused by CO poisoning - induced cytokine release, mitochondrial oxidative stress, inhibition of mitochondrial function, lipid peroxidation, apoptosis, and adaptive immunological responses were revealed to influence the pathogenesis of neuron damage [11]. Previous studies have suggested that several neurodegenerative diseases including Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, and CO poisoning related DNS are related to an imbalance in ROS generation and depletion of antioxidative status. After the balance is disrupted, oxidative stress that may cause delayed neuronal damage is further developed [6,7,11,28,34].

Animal studies have revealed that lipid peroxidation and oxidative stress were involved in the development of CO-mediated delayed neuronal damage and the damage was a time-dependent process. The most significant damage occurs 1–3 days after CO poisoning, and lasts until day 21 [7]. HBOT significantly reduced oxidative stress by increasing the uptake of antioxidative gene expression in animal models of cognitive impairment, and HBOT served as a hormetic agent that initiates antioxidant and cytoprotective genes to protect against mortality in vitro [6,26]. In animal studies, daily HBOT for 2 consecutive weeks also effectively improved the cognitive dysfunction induced by d-galactose. The potential mechanisms of this action indicated that HBOT significantly reduces oxidative stress by attenuating the expression of ageing genes and increasing total antioxidation capability through the activation of superoxide dismutase, glutathione peroxidase, and catalase [6].

In this study, we found a GCS of < 9 and longer duration from CO exposure to HBOT were associated with the development of DNS among CO poisoned patients that received HBOT. Such a finding might be explained by the fact that most patients with poor GCS score and delayed HBOT treatment were those who attempted suicide by burning charcoal. These patients frequently did not leave any suicide note and locked themselves in their bedroom so that prompt rescue could not be provided by the others. As a result, they usually presented to the ED with longer CO exposure and more severe poisoning, and were thus more likely to develop DNS despite the receipt of HBOT. Conversely, a CO poisoning incident with multiple victims was associated with a lower risk of DNS. All events with multiple victims in our study were caused by incomplete water heater combustion at homes, except for one incident of recreational use of charcoal burning by teenagers at a motel. The possible reasons for the inverse association between multiple victims and DNS may be because people with mild symptoms of CO poisoning can alert those living together or call for help at an early stage. Our results indicate that the longer the duration from CO exposure to HBOT, the less favourable the prognosis of CO poisoning. We also analyzed the duration from CO exposure to HBOT (< 6 h, 6–11 h, 12–23 h, 24–47 h, and ≥ 48 h) and found a trend of increasing risk of DNS by the elapsed time. The cut-off point from the ROC curve recommended that HBOT should better be commenced within 22.5 h of CO exposure. We hypothesise that the administration of HBOT within 22.5 h alters the balance between oxidative and antioxidative status, which is the probable mechanism underlying upregulation of antioxidative, cytoprotective, and immediate early gene expressions.

This study has several limitations. Firstly, there has been a steady decline in the number of follow-up visits after discharging a patient from the ED, which has resulted in a decreased ability to detect DNS and may have adversely affected the statistical power of this study. Secondly, we adopted some symptom-based diagnostic criteria of DNS because of the lack of standard ones. Previous studies employed bundle battery of tests [5], Folstein Mini-Mental Status Examination (MMSE) [35], Hamilton Depression Rating Scale (HDRS), Beck Anxiety Inventory, Wechsler Memory Scale-Revised (WMS-R) and Verbal Memory Process Test (VMPT) [36] as the diagnostic criteria of DNS, but these tests were still inconclusive. Thirdly, it was not possible to obtain the baseline neuropsychiatric status of CO poisoned patients prior to their CO exposure. Therefore, although the majority of CO poisoned patients included in this study were young and did not have history of pre-existing neuropsychiatric diseases, we could not completely exclude the possibility that the development of DNS in certain CO poisoned patients might still be attributable to their preclinical dementia process and/or other underlying neuropsychiatric disorders. Fourthly, patients who needed mechanical ventilation support were excluded from this study because our HBO center cannot perform HBOT for patients under mechanical ventilation support. At the same time, some patients were recommended by HBOT physician for HBOT, but they had no will to receive or couldn't complete the full course of HBOT. These patients were mostly of mild or moderate severity, therefore we might not be able to delineate the benefits and optimal timing of HBOT in patients with mild-to-moderate CO poisoning. Finally, since this was a retrospective study and the data were abstracted from chart review, the clinical presentations or medical records might not have been completely documented, which could then lead to the lack of adequate statistical significance to identify certain potential predictors of DNS in CO poisoning patients who received HBOT.

8. Conclusions

We investigated the potential predictors of DNS development among patients with CO poisoning who received HBOT in a medical centre in Taiwan. Multivariate logistic regression analysis revealed that longer duration from CO exposure to HBOT, loss of consciousness, and the presence of multiple victims were independent predictors of DNS development. Moreover, HBOT should be performed as early as possible and preferably within 22.5 h after CO poisoning. The mechanism of the time-dependent benefit of HBOT may be related to oxidative and antioxidative balance after CO poisoning and HBOT. However, such a proposition should be evaluated in further well-designed prospective studies.

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Conflict of interest

The authors declare that they have no competing interests, and have nothing to disclose about financial or non-financial conflicts of interest related to the content discussed in this manuscript.

Author contributions

Shu-Chen Liao, Chen-Chang Yang, conceived the study, and obtained research funding. Shu-Chen Liao, Kun-Ju Yang, Kuo-Cheng Wang and Chen-Chang Yang supervised the conduct of this study and data collection. Shu-Chen Liao, Li-Ying Wu, Yan-Chiao Mao, and Kuo-Cheng Wang provided statistical advice on study design and analyzed the data. Shu-Chen Liao drafted the manuscript, and all authors contributed substantially to its revision. Chen-Chang Yang takes responsibility for the paper as a whole.

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