

Neurocognitive sequelae after carbon monoxide poisoning and hyperbaric oxygen therapy

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Abstract

Carbon monoxide (CO) has been the leading cause of poisoning mortality in many countries and hyperbaric oxygen (HBO) is a widely accepted treatment for CO poisoning. However, some patients with CO poisoning will still develop neurocognitive sequelae regardless of HBO therapy, which can persist since CO poisoning or be present days to weeks after a recovery from CO poisoning. HBO has been used in the prevention and treatment of neurocognitive sequelae after CO poisoning, and some mechanisms are also proposed for the potential neuroprotective effects of HBO on the neurocognitive impairment after CO poisoning, but there is still controversy on the effectiveness of HBO on neurocognitive sequelae after CO poisoning. In this paper, we briefly introduce the neurocognitive sequelae after CO poisoning, summarize the potential predictive factors of neurocognitive sequelae, and discuss the use of HBO in the treatment and prevention of neurocognitive sequelae after CO poisoning.

Key words: carbon monoxide; poisoning; neurocognitive sequelae; persistent neurological sequelae; delayed neurological sequelae; predictors; hypoxia; hyperbaric oxygen; normobaric oxygen; prevention

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INTRODUCTION

Carbon monoxide (CO) is an odorless, colorless, and tasteless gas, and thus it is highly difficult to detect when escaping. CO at a concentration higher than 35 ppm is toxic to humans. CO is the leading cause of poisoning mortality in many countries and may be responsible for more than half of all fatal poisonings worldwide.¹ Although patients can improve over many months, and even up to 1 year, at 6 years after CO poisoning, survivors of CO poisoning usually suffer from long term neurocognitive sequelae related to brain injury.^{2,3} The neurological or cognitive sequelae can occur immediately and persist over time, or the onset can be delayed, and the persistent neurological sequelae (PNS) and delayed neurological sequelae (DNS) are common following acute CO poisoning. It seems that DNS patients have more severe symptoms and worse clinical outcomes than the PNS patients,⁴ and the DNS patients had more significant progress on general cognitive function, psychomotor speed, and visual-spatial ability than did the acute group after continuous hyperbaric oxygen (HBO) therapy.⁵ The symptoms of DNS typically develop after an interval of 2–40 days.⁶ The symptoms of neurocognitive sequelae related to brain injury after CO poisoning include impaired memory, cognitive dysfunction, depression, anxiety, and/or vestibular and motor deficits, and these deficits are evident by 6 weeks.³ Mimura et al.⁷ reported 68.6% of patients had intellectual disturbances and 48.7% had neurologic symptoms at 33 years after CO poisoning, which seems to illustrate the irreversible nature of these deficits. In a study involving 25,912 patients

with CO poisoning, Huang et al.⁸ found the prevalence rate of neurological sequelae after CO poisoning was 9.1% in total, and the rate was 2.3% in the first 2 weeks and 6.2% at the end of the first year. In a more recent study, Huang et al.⁹ found he incidence rates of degenerative diseases of the central nervous system, psychiatric diseases, and other diseases of the nervous system were 23.2, 87.8, and 57.6 per 1000 person-years in patients receiving HBO therapy and 14.9, 59.3, and 34.9 per 1000 person-years in patients without HBO therapy, respectively. In addition, there is evidence showing that the incidences of cognitive deficits and neurologic deficits are 19% and 37% after CO poisoning, respectively.¹⁰ The reported incidence of DNS varies from 0.06% to 40% with the onset 2 to 40 days after CO poisoning,^{11,12} but the information regarding the prevalence of PNS is limited. In a prospective study, Weaver et al.¹³ reported 37% of the participants ($n = 238$) had cognitive sequelae at 6 weeks, of which 59% had PNS and 28% had DNS, a ratio of 2:1 (PNS: initial cognitive dysfunction persists to 6 weeks after CO poisoning; DNS: a decline of at least 1 standard deviation on a neuropsychological subtest score from a prior score). In the current review, we briefly summarized the predictive factors, mechanisms and HBO treatment of neurocognitive sequelae following CO poisoning by searching the PubMed.

PREDICTIVE FACTORS

Some studies have been conducted to investigate the factors predicting the neurocognitive sequelae following CO poisoning. The available factors can be classified as the demograph-



ics, clinical characteristics, blood biochemical parameters, imaging findings and treatments.

Age and sex are two important factors affecting the outcomes of acute CO poisoning. There is evidence showing that old age, male sex and comorbidities were found to be independent predictors for neurocognitive sequelae after CO poisoning.⁹ However, the age and sex as predictors of neurocognitive sequelae after CO poisoning is controversial. The study of Pepe et al.¹⁴ revealed the DNS had no relationship with age and sex.

The clinical characteristics (especially symptoms and signs) may reflect the severity of CO poisoning, and thus it is reasonable that they can be employed for the prediction of neurocognitive sequelae after CO poisoning. Studies have indicated that a longer duration of admission, CO exposure duration > 6 hours, systolic blood pressure < 90 mmHg, Glasgow Coma Scale score < 9, Mini-Mental State Examination score, a lack of pupil reflex and a positive Babinski reflex were associated with the development of DNS or neurological sequelae,¹⁴⁻¹⁷ but voluntary exposure, headache and transient loss of consciousness failed to predict neurocognitive sequelae.¹⁴ Of note, a loss of consciousness was found to be related to the development of neurological sequelae in other studies.^{16,18}

A variety of studies have investigated the blood parameters as the predictors of neurocognitive sequelae after CO poisoning. Available studies have indicated plasma copeptin,¹⁹ serum S-100B protein,²⁰⁻²² neuron-specific enolase,²³ serum lactate level,^{22,24} serum N-terminal pro-B-type natriuretic peptide,²⁵ troponin, creatine kinase,^{18,26} creatine kinase-MB, lactate dehydrogenase,²⁶ serum anion gap,²² serum ubiquitin C-terminal hydrolase-L1,²⁷ and creatine phosphokinase and leukocytosis¹⁴ are related to the neurocognitive sequelae after CO poisoning, and this risk increases with the number of independent predictors.¹⁶ In addition, neuron-specific enolase could improve the prediction accuracy of initial Glasgow Coma Scale.²³ It has been hypothesized that CO poisoning maybe also causes the formation of myelin basic protein (MBP) and DNS occurs due to extensive myelin and neuronal loss.²⁸ Study also shows cerebrospinal fluid-MBP can serve as a sensitive predictor of both the development and outcomes of DNS.²⁹ As mentioned above, serum N-terminal pro-B-type natriuretic peptide, troponin, creatine kinase and creatine kinase-MB are possible prognostic factors for the development of neurocognitive sequelae after CO poisoning, and all these parameters are related to myocardial injury. This is supported by more recent findings that patients having myocardial injury had elevated risk for both PNS and DNS³⁰ and QTc prolongation within 6 hours after CO exposure was a predictor of DNS³¹ However, the application of these parameters in clinical practice warrants more clinical studies, and there is still controversy on several blood parameters (such as lactate level¹⁴). Thom et al.³² used Luminex-based technology to determine the concentration of 180 proteins in 63 suspected CO poisoning patients, and they concluded that the CO pathophysiology was complex and this technique had insufficient power to identify reliable plasma predictors of neurological sequelae although their findings support a view that CO exposure caused acute inflammatory events in humans. Of note, some studies fail to found the relationship between carboxyhemoglobin and neurocognitive

sequelae after CO poisoning although carboxyhemoglobin is a common blood parameter that is detected on admission and used to diagnose CO poisoning and assess the severity of CO poisoning.^{14,15}

Several studies have also investigated the relationships of treatments after CO poisoning with neurocognitive sequelae. In the study of Lin et al.,³⁰ use of tranquilizer and treatment in intensive care unit increased the risk for PNS. Chang et al.³³ found treatment in the intensive care unit because of prolonged loss of consciousness was the independent risk factor for DNS and rescue by a ventilator was independently associated with PNS. The intubation requirement was also found to be a possible prognostic factor for development of DNS after CO poisoning.¹⁸ A treatment for CO poisoning is HBO therapy, studies also assess the relationship between HBO therapy and neurocognitive sequelae after CO poisoning, but there is still controversy on this issue. Chang et al.³³ found HBO therapy did not affect the incidence of both DNS and PNS. In addition, there is evidence showing that more sessions of HBO therapy was associated with the development of DNS¹⁵ and HBO therapy seemed to increase the risk for neurocognitive sequelae.⁹ However, in a study with small sample size, Chan et al.¹⁸ found a 100% protective effect of HBO therapy against development of DNS in patients with severe CO poisoning (24 patients receiving HBO therapy did not develop DNS).

Magnetic resonance imaging (MRI) and computed tomography (CT) are the common tools used in the assessment of brain injury.³⁴⁻³⁶ It has been confirmed that CO poisoning may result in focal and generalized neuroanatomical abnormalities observed on MRI and CT. Imaging examinations can not only be used for the assessment of early neurological lesions after CO poisoning, but also be employed to aid the diagnosis of neurocognitive sequelae. The imaging findings of the brain after CO poisoning and those in patients with neurocognitive sequelae have been described elsewhere.^{37,38} Here, we only discuss the predictive value of imaging findings of the brain. Several studies have shown that the presence of acute brain lesions on MRI was significantly associated with the development of DNS^{39,40} and fractional anisotropy value of white matter on diffusion tensor imaging is also predictive for DNS.^{41,42} Head CT findings indicating hypoxic encephalopathy and regional cerebral blood flow are also predictive for the development of DNS.^{26,43} Proton magnetic resonance spectroscopy can monitor the neurochemical disturbances to assess the pathophysiology of CO poisoning. It was reported that the presence of a lactate peak was a predictor for a poor long-term outcome, and proton magnetic resonance spectroscopy within 1 week after CO poisoning could be employed to predict DNS development.⁴⁴ The striatal dopamine transporter binding measured by single photon emission CT with ^{99m}Tc-TRODAT could help to predict the development of DNS.⁴⁵ However, Ozcan et al.⁴⁶ found the white matter lesions which progress to demyelination and end up in neuropsychological sequelae could not always be diagnosed by early CT and MRI in CO poisoning.

Several investigators also investigate the predictive value of polymorphism for neurocognitive sequelae in patients after CO poisoning. Liang et al.⁴⁷ investigated the PARK2 polymorphism

and clinical outcome in patients following CO poisoning and found the allelic variant of rs1784594 was a risk factor for DNS. In the study of Li et al.,⁴⁸ results showed variants at NRXN3 was associated with DNS after acute CO poisoning. Hopkins et al.³ investigated the APOE genotypes in 86 of 152 CO-poisoned patients and their results showed HBO therapy reduces cognitive sequelae after CO poisoning in the absence of the *epsilon4* allele.

MECHANISMS

The pathogenesis of neurocognitive sequelae is still poorly understood, and several mechanisms have been proposed: (1) hypoxia: It is well known that the affinity of CO to hemoglobin is 300 times higher than that of oxygen, and the release of CO from carboxyhemoglobin is 3600 times slower than that of oxygen, which may cause hypoxia following CO poisoning, which was proposed as a factor related to neurocognitive sequelae.¹⁰ The termination of CO exposure or treatment for CO poisoning seems to be an oxygenation, which mimics the ischemia/reperfusion injury to the brain.¹⁰ In addition, CO may also bind to the mitochondrial cytochrome oxidase to inhibit mitochondrial respiration, which reduces ATP production, directly or indirectly causing damage to cells; the extended and generalized inhibition of cytochrome oxidase could explain the persistence of different symptoms after the normalization of carboxyhemoglobin levels.⁴⁹ Although CO induced hypoxia plays a role in the pathogenesis of CO poisoning, its contribution is likely much less than previously suspected since many of the second order effects described are not completely explained by hypoxemic hypoxia.⁵⁰ (2) Immune-mediated injury: CO poisoning may also causes adduct formation between MBP and malonylaldehyde, resulting in an immunological cascade.²⁸ Cerebrospinal fluid-MBP can serve as a sensitive predictor of both the development and outcomes of DNS.²⁹ (3) Metabolic dysfunction: CO poisoning may cause metabolic dysfunction in the brain, affecting the neurological dysfunction.^{44,51} (4) Cytotoxicity of neurotransmitter: it has been found that glutamate increases significantly after CO poisoning and glutamate activates N-methyl-D-aspartate receptors, enhancing cellular dysfunction and apoptosis.^{52,53} (5) Reactive oxygen species: CO poisoning may significantly increase the reactive oxygen species production in the brain and weaken antioxidant systems,⁵⁴ and lipid peroxidation was found to be involved in the memory impairment of CO-induced delayed neuron damage.⁵⁵ In addition, anti-oxidative strategies have also employed for the treatment of acute CO poisoning⁵⁶ and its neurocognitive sequelae,⁵⁷ and Mannaioni et al.⁵⁸ proposed the addition of free radical scavengers (such as glutathione, acetylcysteine, and tempol) to the standardized treatment of acute CO poisoning. (6) Cell death: CO poisoning may cause cell death via different ways (apoptosis and autophagy), predisposing brain injury.⁵⁸⁻⁶¹ (7) Others: CO may also induce neuronal ion channel dysfunction⁶² and inflammation,^{63,64} which also contribute to the pathogenesis of neurocognitive sequelae. In addition, the nicotinic cholinergic system is also related to DNS.⁶⁵

EFFECTS OF HYPERBARIC OXYGEN THERAPY

HBO therapy refers to an intervention in which an individual

breathes near 100% oxygen while inside a hyperbaric chamber that is pressurized to greater than sea level pressure (1 atmosphere absolute [ATA]). Although CO poisoning is an indication to HBO therapy and there is evidence showing HBO therapy is associated with lower mortality,^{66,67} the effects of HBO therapy on the development of neurocognitive sequelae remain controversial.^{9,13} In the following section, we summarized the use of HBO in the therapy and the prevention of neurocognitive sequelae.

HBO treatment

In as early as 1985, Myers and colleagues⁶⁸ reported 12.1% neurological sequelae in a series of 82 patients treated with normobaric oxygen. Ten patients returned with headaches, irritability, personality changes, confusion, and loss of memory. These recurring symptoms resolved rapidly with HBO therapy. They recommend that HBO be used whenever CO symptoms recur.⁶⁸ Thereafter, increasing institutes employ HBO for the treatment of neurocognitive sequelae after CO poisoning, and some case reports, clinical studies and animal studies published confirm the neuroprotective effects of HBO on them.⁶⁹⁻⁷¹ Chang et al.⁷² conducted HBO therapy in a series of patients with DNS and found 8–40 sessions of HBO therapy was able to decrease the severity of impairment in DNS patients. After reviewing literature, Lee et al.⁷³ concluded that HBO may be effective in treating DNS after CO poisoning. Spagnolo et al.⁷⁴ even reported the delayed HBO therapy improved the DNS in a 62-year-old man suffering from CO poisoning who did not receive HBO therapy at baseline. Another advantage of HBO therapy is that it is relatively safe for pregnant women⁷⁵ and children,⁷⁶ and it can also be used during mechanical ventilation.⁷⁷

Of note, there is limited evidence of the efficacy of HBO treatment, and supportive and symptomatic treatment is recommended for patients diagnosed with neurocognitive sequelae after CO poisoning.⁷⁸ Some investigators attempt to use HBO therapy in combination with other strategies in the treatment of neurocognitive sequelae after CO exposure. There is evidence showing that N-butylphthalide is protective on CO poisoning in animals⁷⁹ and Xiang et al.⁸⁰ found combined application of N-butylphthalide and HBO could significantly improve the cognitive dysfunction of patients with DNS and have great clinical efficacy. In addition, HBO therapy combined with risperidone,⁸¹ acupuncture,⁸² high dose ganglioside,⁸³ edaravone,⁸⁴ dexamethasone⁸⁵ and hypothermia⁸⁶ is also found to improve the neuropsychological functions of patients after CO poisoning.

Prevention with HBO

As above mentioned, several factors are closely related to the development of neurocognitive sequelae after CO poisoning, in which HBO therapy is an important one. Based on the findings from a clinical study, Thom et al.⁶ recommended HBO treatment in acute CO poisoning to decrease the incidence of DNS after CO poisoning. They further investigated the potential mechanism and found the prophylactic effect of HBO therapy on DNS was related to the inhibition of MBP induced lymphocyte activation after CO poisoning.⁸⁷ Early



HBO therapy is employed to prevent the development of neurocognitive sequelae. Weaver et al.¹³ proposed emergent HBO therapy within 24 hours appeared to reduce the risk of cognitive sequelae after acute CO poisoning. For children with CO poisoning, HBO therapy affected the neuropsychological symptoms⁸⁸ and Gozubuyuk et al.⁷⁶ proposed HBO therapy should be performed within first 6 hours of poisoning if possible, and HBO therapy should be repeated within 6 to 8 hours if loss of consciousness persists after HBO therapy, which may improve the prognosis. After literature reviewing, Lee et al.⁷³ also concluded immediate administration of HBO during acute CO intoxication may prevent neuropsychiatric sequelae. Although the effects of HBO vs normobaric oxygen therapy on long-term neurocognitive outcomes after CO poisoning remain unclear, the 2017 American College of Emergency Physicians (ACEP) Clinical Policy on CO Poisoning provides level B recommendations that HBO or high-flow normobaric oxygen therapy should be used for acute CO-poisoned patients.⁸⁹ In addition, some investigators also investigate the role of oxygen partial pressure in the therapeutic effects of oxygen. In an *in vitro* study, Jurič et al.⁹⁰ compared the effectiveness of normobaric oxygen vs. HBO in the treatment of CO poisoning, and their results showed oxygen therapy (1 hour) disclosed pressure- and time-dependent efficacy in restoring astrocytic mitochondrial function and the prevention of apoptosis. In the study of Thom et al.,⁶ 7 of 30 patients (23%) developed DNS after treatment with ambient-pressure oxygen (DNS occurred 6 ± 1 days after poisoning), but none developed sequelae in 30 patients after HBO treatment. Lin et al.⁹¹ conducted a systematic review and meta-analysis of randomized controlled trials to investigate the therapeutic efficacy of normobaric and HBO on neuropsychometric dysfunction after CO poisoning. They conclude that patients receiving HBO treatment had a lower incidence of neuropsychological sequelae (including headache, memory impairment, difficulty concentrating, disturbed sleep, and DNS) as compared to those treated with normobaric oxygen. Hampson et al compared two hyperbaric treatment protocols for CO poisoning (2.4 ATA, 100% oxygen, 90 minutes vs. US Air Force CO protocol [3.0 ATA maximum pressure])⁹² and results showed there was no significant difference in the proportion of patients with abnormal neurological testing at 14–21 days (4/18 vs. 2/12; $P = 0.71$). In addition, the effect on headache after CO poisoning was also similar between HBO therapy and normobaric oxygen therapy.⁹³

However, there is still controversy about the efficacy of HBO on development of neurocognitive sequelae after CO poisoning. In patients with initial impairment of consciousness after CO poisoning who received 4-hour normobaric oxygen treatment, HBO therapy seemed to have no influence on the development of neuropsychiatric sequelae.⁹⁴ On the basis of six randomized controlled trials, Buckley et al.⁹⁵ speculated that the efficacy of HBO for the prevention of neurological sequelae was still uncertain, which might be ascribed to the significant methodologic and statistical heterogeneity. Gilmer et al.⁹⁶ also found HBO was not effective in preventing neurologic sequelae in mice and there was no benefit of HBO over normobaric oxygen following severe CO poisoning. Scheinkestel et

al.⁹⁷ also compared HBO with normobaric oxygen in patients with CO poisoning, and found more patients receiving HBO required additional treatments; more HBO treated patients had a worse outcome in the learning test and a greater number of abnormal test results at completion of treatment; DNS was restricted to HBO treated patients ($P = 0.03$), but no outcome measure was worse in normobaric oxygen group. Two randomized controlled trials also failed to show the evidence of superiority of HBO over normobaric oxygen in patients with transient loss of consciousness, and two HBO sessions were associated with worse outcomes than one HBO session in comatose patients.⁹⁸ In a population-based cohort study involving 24,046 patients with CO poisoning, Huang et al.⁹ found the risk for neurologic sequelae was higher in patients with CO poisoning who received HBO therapy than in those who did not after adjusting for age, sex, and other confounding factors, and similar findings were observed after stratifying the patients by age, sex, underlying comorbidities, and monthly income. Moreover, they found the increased risk was most prominent in the first 2 weeks and remained significant up to 6 months later. In addition, the effectiveness of HBO therapy still remains unclear in preventing dementia.⁹⁹

CONCLUSIONS

CO has been the leading cause of poisoning mortality in many countries. Although great progress has been achieved in the treatment of CO poisoning, some patients will still develop neurocognitive sequelae after CO poisoning, which can persist since CO poisoning or be present days to weeks after a recovery from CO poisoning. Administration of supplemental oxygen is the primary treatment for CO poisoning, but the delivery of supplemental oxygen via HBO remains inconclusive as a primary treatment strategy. Moreover, the effectiveness of HBO in the prevention and treatment of neurocognitive sequelae is still controversial. A recent study with large sample size brings promise to the use of HBO in the therapy of CO poisoning, but this study remains distant from the ideal of a large blinded multicenter randomized controlled trial. As shown by Cowl,¹⁰⁰ “it is time to justify HBO delivery for CO poisoning.”

Author contributions

Study design: CHH, WWL, YYZ; data search and manuscript drafting: KN, CHH; manuscript revising: YYZ, NZ, XJS. All authors approved the final version of the manuscript for publication.

Conflicts of interest

The authors have no conflicts of interests to declare.

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