

Carbon Monoxide Poisoning

Risk Factors for Cognitive Sequelae and the Role of Hyperbaric Oxygen

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Rationale: Carbon monoxide poisoning is common and causes cognitive sequelae. Hyperbaric oxygen (HBO₂) reduces cognitive sequelae incidence, but which patients may benefit from HBO₂ is unclear.

Objectives: Risk factor determination for 6-wk cognitive sequelae from CO poisoning and risk modification with HBO₂.

Methods: Patients were from a randomized controlled trial, enrolling acutely CO-poisoned patients more than 15 years of age. Patients eligible but not enrolled in the randomized trial, and not receiving HBO₂, were followed during the study interval. In patients not receiving HBO₂, we performed univariate analyses including risk factors identified by randomized trial subgroup analyses. A multivariable analysis was performed using univariate results with and without HBO₂.

Measurements and Main Results: In 163 patients not receiving HBO₂, 68 (42%) manifested sequelae. Risk factors for sequelae from subgroup analyses were loss of consciousness, age of 36 years or more, and carboxyhemoglobin levels greater than or equal to 25%. By univariate analyses, risks for sequelae were age of 36 years or more (odds ratio [OR], 2.6; 95% confidence interval [CI], 1.3–4.9; *P* = 0.005), and exposure intervals greater than or equal to 24 hours (OR, 2.4; 95% CI, 1.2–4.8; *P* = 0.019). Including 75 patients receiving HBO₂, cognitive sequelae was reduced in patients age of 36 years or more (OR, 0.3; 95% CI, 0.2–0.6; *P* < 0.001). Exposure intervals greater than or equal to 24 hours are an independent risk factor for sequelae (OR, 2.0; 95% CI, 1.0–3.8; *P* = 0.046).

Conclusions: HBO₂ oxygen is indicated for patients with acute CO poisoning who are 36 years or older or have exposure intervals greater than or equal to 24 hours. In addition, subgroup analyses support that patients with loss of consciousness or higher carboxyhemoglobin levels warrant HBO₂.

Keywords: carbon monoxide poisoning; hyperbaric oxygen therapy; cognitive outcome; neuropsychological outcome

Carbon monoxide poisoning is common, and causes cognitive sequelae (1). A recent double-blind clinical trial demonstrated a 46% reduction in cognitive sequelae 6 weeks after poisoning in patients treated with hyperbaric oxygen (HBO₂) therapy compared with normobaric oxygen (1). An editorialist stated, “Hyperbaric oxygen should be the standard of care for acute CO poisoning” (2).

Selection criteria for HBO₂ in patients with acute CO poisoning are empiric. The accompanying editorial to our randomized trial (1) recommended that patients with a carboxyhemoglobin (COHb) level greater than 25%, or a base excess lower than –2 mmol/L, should receive HBO₂ (3). Others recommend HBO₂

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Carbon monoxide (CO) poisoning is common and causes cognitive sequelae. Hyperbaric oxygen reduces cognitive sequelae, but which patients need hyperbaric oxygen is unclear.

What This Study Adds to the Field

HBO₂ oxygen is indicated for patients with acute CO poisoning who are 36 years or older or have exposure intervals greater than or equal to 24 hours. In addition, subgroup analyses support that patients with loss of consciousness or higher carboxyhemoglobin levels warrant HBO₂.

if the COHb level exceeds 25% (4, 5) or 40% (6), regardless of signs or symptoms. In addition, loss of consciousness due to CO poisoning is an independent criterion for HBO₂ (5–7). Clearly, there are differing opinions regarding which CO-poisoned patients should receive HBO₂ (5).

We reasoned that if we could identify available clinical criteria that were linked with higher risk for poisoning-related cognitive sequelae, and if HBO₂ reduced that risk, then we could use that information to make recommendations regarding who should receive HBO₂.

In the present study, we assessed risk for cognitive sequelae in patients we have followed prospectively who were not treated with HBO₂ (both randomized-trial [1] and nonrandomized-trial patients). We then assessed the risk-reduction in those patients treated with HBO₂ from our randomized trial (1). To emphasize the importance of reducing the cognitive sequelae incidence with HBO₂, we also assessed the magnitude of cognitive dysfunction in those patients with cognitive sequelae. Some of the results of this study have been previously reported in the form of an abstract (8).

METHODS

Data from patients enrolled in our randomized clinical trial of acute CO poisoning (1) and nonrandomized-trial patients were included in this study. Nonrandomized-trial patients were derived from those eligible for our randomized trial, but who declined enrollment (1), or from those who were ineligible for the randomized trial because they presented more than 24 hours after poisoning (Table 1). The prime end-point of our randomized trial was cognitive sequelae 6 weeks after poisoning. (1) None of the nonrandomized-trial patients received HBO₂.

Patients were eligible for study enrollment if they had a documented CO exposure (elevated COHb levels or measured elevations in ambient CO concentrations), and any of the following: loss of consciousness, confusion, headache, malaise, fatigue, forgetfulness, dizziness, visual disturbances, nausea, vomiting, cardiac ischemia, or metabolic acidosis (calculated base excess < –2.0 mmol/L, or a blood lactate level > 2.5 mmol/L). Nineteen percent (17/91) of nonrandomized-trial patients

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TABLE 1. REASONS FOR NON-PARTICIPATION IN RANDOMIZED TRIAL

Reason	No. of patients (n = 97)
Interval since end of exposure > 24 h	36
Inconvenience	20
Cost of treatment	9
Issues related to chamber or hyperbaric oxygen	6
Did not wish to participate	6
Cost of transport	5
Unable to consent and no surrogate*	4
Referring physician declined	3
No identified reason	2

* These four patients gave consent for this long-term study but not for the randomized controlled trial (1).

were not treated with supplemental oxygen because their COHb levels were normal, due to delay in presentation for medical care. Poisoning was confirmed by evidence of a CO poisoning source, the presence of symptoms, and no other plausible explanation for their symptoms.

Patients were recruited from Utah, Idaho, and Wyoming from November 1992 through February 1999. The institutional review board at LDS Hospital approved this prospective outcome study. Written informed consent was obtained from patients or their surrogates before enrollment.

Data Collection

At enrollment, data concerning demographics, physiology, comorbid conditions, oxygen therapy, and medications, together with details of CO poisoning, were recorded. Patients' cognitive outcomes were reassessed at 6 weeks, 6 months, and 12 months after CO poisoning.

A battery of neuropsychological tests identical to that used in our randomized trial (1) consisting of general orientation, digit span (9), Trail Making (Parts A and B) (10), digit-symbol (9), block design (9), and story recall (11) subtests was administered initially and at 6 weeks, 6 months, and 12 months. All tests were reliable and valid; were administered using standardized formats (12) in private, quiet examination rooms; and were converted to demographically corrected standardized T-scores (mean = 50; standard deviation = 10) (13, 14). *A priori*, cognitive sequelae were considered to be present if any 6-week neuropsychological subtest T-score was greater than two standard deviations below the mean, or if two or more subtest T-scores were each greater than one standard deviation below the mean. If the patient complained of memory, attention, or concentration difficulties, the required neuropsychological test decrement was decreased to greater than one standard

deviation below the mean of demographically corrected standardized T-scores on any one subtest (13, 14). The magnitude of cognitive impairment in patients with cognitive sequelae at 6 weeks, 6 months, and 12 months after CO poisoning was assessed by summing the number of standard deviations greater than one standard deviation below the mean for all subtest T-scores (15).

The oxygen therapy of randomized trial patients was described previously (1, 16). Briefly, patients breathed nonbreather reservoir facemask oxygen followed by HBO₂ or continued facemask oxygen. Intubated patients breathed 100% oxygen before and during HBO₂ or the normobaric oxygen sessions. The mean duration of total high concentration oxygen therapy through chamber session one was 6.9 hours for the normobaric oxygen group and 7.0 hours for the HBO₂ group (1, 16). The patients treated with HBO₂ were initially compressed to 3.0 atmospheres absolute (atm abs) (304 kPa) for 50 minutes, followed by 60 minutes at 2.0 atm abs (203 kPa). In 6- to 12-hour intervals, they received two additional HBO₂ sessions at 2.0 atm abs for 90 minutes. Five-minute air breathing periods were provided every 25 minutes while at 3.0 atm abs and every 30 minutes while at 2.0 atm abs (1). Eighty-one percent (74/91) of nonrandomized-trial patients were treated with supplemental oxygen.

Our study prime endpoint was the incidence of cognitive sequelae at 6 weeks. Also, we reported CO-related cognitive sequelae at 6 months and 12 months after poisoning. *A priori* we assumed that cognitive sequelae developing after 6 weeks would not be caused by CO poisoning (1, 17-20).

Statistical Analysis

We conducted univariate analyses on data from all patients who did not receive HBO₂ (n = 163) to identify potential risk factors for cognitive sequelae. In these univariate analyses, we included risk factors identified from subgroup analyses from our randomized trial (1) that suggested associations with 6-week cognitive sequelae (Table 2). The following potential risk factors were included in the univariate analyses: study arm (nonrandomized trial, normobaric randomized trial, or hyperbaric randomized trial), sex, age, years of formal education, and speaking English. Also included were: history of hypertension, psychological disorder, suicide attempt, etiology of poisoning, if work-related, interval of exposure to CO or whether exposure was intermittent. In addition we included: loss of consciousness and duration, initial symptoms (headache, nausea or vomiting, weakness, malaise, or lethargy, dizziness, and difficulties with memory), method of oxygen therapy delivery, initial COHb level, estimated COHb level at end of CO exposure, initial base excess, interval from end of CO exposure until COHb measurement, interval from end of CO exposure until clinical oxygen therapy, and duration of clinical oxygen therapy. The estimated COHb level was calculated using the interval between CO

TABLE 2. COGNITIVE SEQUELAE BY SUBGROUPS (POST HOC ANALYSIS)

Subgroup: no./total no. (%)	Randomized Trial			Nonrandomized Trial (n = 91)
	Hyperbaric Oxygen (n = 75)	Normobaric Oxygen (n = 72)	P Value*	
Loss of consciousness				
Loss of consciousness	8/37 (22)	18/37 (49)	0.03	14/36 (39)
No loss of consciousness	10/38 (26)	13/35 (37)	0.45	24/55 (44)
Age				
< 36 yr	9/40 (23)	12/38 (32)	0.45	16/51 (31)
≥ 36 yr	9/35 (26)	19/34 (56)	0.02	22/40 (55)
Initial carboxyhemoglobin level				
< 25 percent	11/39 (28)	13/34 (38)	0.46	27/65 (42)
≥ 25 percent	7/36 (19)	18/38 (47)	0.01	4/12 (33)
Initial base excess				
< -2 mEq/L	7/23 (30)	11/19 (58)	0.12	5/16 (31)
≥ -2 mEq/L	8/41 (20)	14/44 (32)	0.22	13/32 (41)
Interval of carbon monoxide exposure				
< 24 h	18/70 (26)	26/63 (41)	0.07	16/54 (30)
≥ 24 h	0/5 (0)	5/9 (56)	0.09	22/37 (60)

Because of rounding, not all percentages total 100.

* The P values represent comparison between the hyperbaric oxygen and normobaric oxygen groups from a randomized controlled trial (1), not the nonrandomized trial group.

exposure ending to the measurement of the initial COHb level, while using a COHb half-life equal to 320 minutes while breathing air (21) and 74 minutes while breathing normobaric oxygen (22).

Fisher's exact tests were conducted on categorical factors to determine if the incidence of cognitive sequelae varied across factor levels. For continuous factors, two-sampled *t* tests were performed to determine if mean values with and without cognitive sequelae were different. Skewed factors were log-transformed before conducting two-sample *t* tests, and geometric means were reported. Factors statistically significant at a 0.1 two-sided significance level, and factors often used to make treatment decisions for acute CO poisoning (e.g., loss of consciousness, initial COHb levels, and initial base excess measurements), were analyzed further.

The initial COHb level and base excess are continuous factors, which are used for HBO₂ treatment decisions. They were categorized as COHb level less than 25% or higher than or equal to 25% and base excess lower than -2 mmol/L or greater than or equal to -2 mmol/L. (3) Analysis on each statistically significant continuous factor ($P < 0.1$) was performed to assess if a factor would be more appropriately represented as a categorical variable. For this analysis, the factor was categorized into intervals with similar number of cases. Logistic regression was performed with 6-week cognitive sequelae as the dependent variable and the newly categorized factor as the independent variable. The coefficients from the logistic regression model versus the midpoint of the categorized intervals were plotted. A factor remained as continuous if its associated plot was linear; otherwise, final categories were determined by reviewing the plot of sequelae rates across categories. In addition, receiver operating characteristic (ROC) curves confirmed were created to confirm the appropriateness of a categorized factor.

Multivariable logistic regression using the backward stepwise likelihood ratio technique was performed on the remaining factors. From this multivariable analysis we retained potential risk factors with $P < 0.05$. The multivariable analysis was then repeated for these identified risk factors along with their two-way interactions. This latter analysis determined those risk factors and interactions associated with 6-week cognitive sequelae ($P < 0.05$). Of the univariate factors retained in the multivariable analyses, if two or more of these factors were highly associated, then only one factor was selected for further modeling to avoid collinearity.

To determine if HBO₂ reduced risk for cognitive sequelae, we performed separate multivariable logistic regression using the backward stepwise likelihood ratio technique on the entire sample ($n = 238$) with each identified risk factor, the specific therapy (HBO₂ versus no HBO₂), and the interaction between therapy and risk factor as independent variables. All risk factors and risk factor-therapy interaction from each multivariable analysis with $P < 0.1$ were retained. A final multivariable logistic regression analysis using the retained risk factors and risk factor-treatment interactions was performed. Risk factors, therapy, and interactions with $P < 0.05$ were considered significant and used to determine efficacy of HBO₂. All *P* values are two-sided.

RESULTS

A total of 238 patients were enrolled in this study; 147 patients were enrolled in the randomized trial, 75 of whom received HBO₂ (1), 72 normobaric oxygen (1), and 91 who were eligible for, but were not enrolled in, the randomized trial (Table 1). Of the 238 patients, cognitive sequelae were found in 37% (87/238) at 6 weeks, 26% (54/204) at 6 months, and 17% (35/211) at 12 months after acute CO poisoning. (The reason we had more patients follow-up at 12 months compared with 6 months was award of a grant that funded 6- and 12-month follow-up. Grant funding was received after some patients had passed their 6-month follow-up evaluation, but not their 12-month evaluation.)

Baseline characteristics of the 75 patients treated with HBO₂ (1), those not treated with HBO₂ ($n = 163$), and the total group of patients ($n = 238$) are reported in Table 3. Of the 163 patients not treated with HBO₂, 42% (69/163) had cognitive sequelae at 6 weeks, 30% (44/146) at 6 months, and 18%

(27/149) at 12 months. Of the group treated with HBO₂ ($n = 75$), 24% (18/75) had cognitive sequelae at 6 weeks, 17% (10/58) at 6 months, and 14% (9/62) at 12 months (1). Of these 163 patients not treated with HBO₂, there was no difference in cognitive sequelae by treatment group (nonrandomized versus randomized normobaric oxygen). In the 146 patients treated with oxygen (but not HBO₂), 60 (41%) had 6-week cognitive sequelae. In the 17 patients that were not treated with supplemental oxygen, 9 (53%) had 6-week sequelae.

In patients with cognitive sequelae, the magnitude of the cognitive impairment 25 to 75% interquartile range was one to four standard deviations below the mean (median 2.0) of demographically corrected T-scores (mean of 50, stand deviation of 10; Figure 1). The magnitude of cognitive impairment was the same regardless of patient group (hyperbaric or normobaric oxygen or nonrandomized trial). There was no difference in the magnitude of cognitive sequelae at 6 weeks, 6 months, or 12 months after poisoning.

Risk Factors for Cognitive Sequelae without HBO₂

Univariate analyses performed on data from the 163 patients not treated with HBO₂ identified the following potential risk factors for 6-week cognitive sequelae: age of 36 years or more, CO exposure interval 24 hours or longer, intermittent exposure, and initial memory complaints (Table 4). Eighty-nine percent (41/46) of patients with CO exposure interval 24 hours or longer had intermittent CO exposures.

The following were not risk factors for 6-week cognitive sequelae: sex, education level, poisoning etiology, if work-related, interval between the end of CO exposure and clinical oxygen therapy, duration of clinical oxygen, loss of consciousness, initial COHb level, estimated COHb level when CO poisoning ended, hypertension, history of psychological disorder, and initial symptoms of headache, nausea or vomiting, weakness, malaise, or lethargy, and dizziness.

Results did not change when subsequent analyses omitted: (1) 33 patients with COHb levels less than 10%, (2) 26 with suicide attempt, or (3) 46 with CO exposure duration longer than 24 hours.

Multivariable Logistic Regression without HBO₂

The factors included for the multivariable logistic regression were age of 36 years or more, CO exposure interval 24 hours or longer, initial memory complaints, loss of consciousness duration (< 60 min, ≥ 60 min), initial COHb level 25% or higher, and initial base excess lower than -2 mmoles/L.

Only age greater than or equal to 36 years (odds ratio [OR], 2.6; 95% confidence interval [CI], 1.3-4.9; $P = 0.005$), and CO exposure interval 24 hours or longer (OR, 2.4; 95% CI, 1.2-4.8; $P = 0.02$) remained as risk factors for 6-week cognitive sequelae.

Risk Factor Reduction with HBO₂

The multivariable logistic regression analysis indicated that patients 36 years or older treated with HBO₂ had reduced 6-week cognitive sequelae rates (OR, 0.3; 95% CI, 0.2-0.6; $P < 0.001$). In those patients without loss of consciousness or COHb levels less than 25%, 31 were 36 years or older. Therefore, in our study population, 31 of 238 patients (13%), would have warranted HBO₂, in the absence of loss of consciousness or COHb criteria. A CO exposure interval 24 hours or longer is an independent risk factor for cognitive sequelae regardless of HBO₂ (OR, 2.0; 95% CI, 1.0-3.8; $P = 0.046$). Our sample size was insufficient to demonstrate a reduced sequelae rate with HBO₂ in those patients with a CO exposure interval 24 hours or longer. However, no patient with a CO exposure interval

TABLE 3. BASELINE CHARACTERISTICS OF THE CARBON MONOXIDE-POISONED PATIENTS

Characteristics	Hyperbaric Oxygen (n = 75)	No Hyperbaric Oxygen (n = 163)	All Patients (n = 238)
Age, yr	35 ± 10	36 ± 15	36 ± 14
Female sex, % (no.)	29 (22)	39 (63)	36 (85)
English as primary language, % (no.)	96 (72)	95 (155)	95 (227)
Education level, yr	12 ± 3	13 ± 3	13 ± 3
Suicide attempt, % (no.)	36 (27)	16 (26)	22 (53)
Median interval of CO exposure, h (25th–75th percentile)	4 (2-9)	8 (3-38)	7 (2-16)
Intubated, % (no.)	8 (6)	8 (13)	8 (19)
Source of CO, % (no.)			
Internal combustion engine	61 (46)	36 (58)	44 (104)
Furnace or heater	36 (27)	56 (91)	50 (118)
Other*	3 (2)	9 (14)	7 (16)
Intermittent exposure, % (no.)	9 (7)	26 (43)	21 (50)
Initial symptoms, % (no.)			
Headache	77 (58)	79 (128)	78 (186)
Nausea or vomiting	63 (47)	60 (97)	61 (144)
Weakness or lethargy	59 (44)	53 (86)	55 (130)
Dizziness	53 (40)	53 (86)	53 (126)
Difficulties with memory or confusion	40 (30)	26 (42)	30 (72)
Loss of consciousness, % (no.)			
< 5 min	49 (37)	45 (73)	46 (110)
≥ 5 min and < 60 min	11 (8)	20 (32)	17 (40)
≥ 60 min	24 (18)	12 (20)	16 (38)
≥ 60 min	15 (11)	13 (21)	13 (32)
Median interval between end of exposure to CO and initial COHb measurement, h (25th–75th percentile) [no.] [†]	1 (1-2)	2 (1-3) [146]	1 (1-3) [221]
Initial COHb level, % [no.] [‡]	25 ± 10	20 ± 12 [149]	22 ± 11 [224]
Estimated COHb level at end of exposure to CO, % [no.] ^{‡‡}	37 ± 14 [74]	35 ± 14 [125]	35 ± 14 [199]
Initial base excess, mmol/L [no.] [‡]	-4 ± 5	-3 ± 4 [129]	-3 ± 4 [204]
Median interval between end of exposure to CO and initiation of clinical oxygen treatment, h (25th – 75th percentile)	1 (0-1)	1 (0-2)	1 (0-2)
Duration of clinical oxygen treatment, h [no.] ^{§§}	4 ± 3	5 ± 5 [159]	5 ± 4 [234]
Baseline comorbidities			
Hypertension, % (no.)	5 (4)	11 (18)	9 (22)
Psychiatric history, % (no.)	28 (21)	26 (43)	27 (64)
History of cardiovascular disease, % (no.)	0 (0)	4 (6)	3 (6)
Diabetes, % (no.)	0 (0)	2 (3)	1 (3)
History of neurological disease, % (no.)	1 (1)	2 (4)	2 (5)

Definition of abbreviation: COHb, carboxyhemoglobin.

Plus-minus values are means ± 1 SD. Because of rounding, not all percentages total 100.

* Other sources of CO exposure were 12 using charcoal grills indoors, and 4 patients with smoke inhalation.

† Bracket symbols [] denote number of patients if different than total number in column.

‡ Estimated from initial COHb level (if level > 3%), time from end of exposure until clinical oxygen using half-life of 320 min (20), and time from clinical oxygen until measurement of initial COHb level using half-life of 74 min (21).

§§ Refers to clinical oxygen therapy before hyperbaric oxygen therapy (for the hyperbaric oxygen group).

24 hours or longer treated with HBO₂ had cognitive sequelae (n = 5).

DISCUSSION

We demonstrated previously that HBO₂ reduces cognitive sequelae from acute CO poisoning, and that CO-related sequelae are common after poisoning (1). In that report, we did not identify risk factors for CO-related cognitive sequelae. In the present study, only two risk factors for cognitive sequelae were identified by univariate and multivariable analyses: older age and longer CO poisoning interval. The presence of identified factors increase the patient's risk for sequelae, but patients without these risk factors may still develop cognitive sequelae.

Results indicate that symptomatic CO-poisoned patients 36 years or older should receive HBO₂, regardless of loss of consciousness, initial COHb, or base excess levels. Older poisoned patients have a higher risk for cognitive sequelae, possibly analogous to risk for worse outcomes in older patients with traumatic brain injury (23). Possible age-related mechanisms that influence recovery after brain injury include apoptosis (24), and older individuals with closed head injury possessing the apolipoprotein epsilon 4 genotype (25).

Longer CO exposure intervals were associated with increased risk for cognitive sequelae, in agreement with some investigations (26), but not others (27). We could not estimate the absolute CO exposure interval in some patients, yet, even if intermittent, the longer CO exposure intervals were associated with increased risk for sequelae. None of five patients with poisoning exposures 24 hours or longer treated with HBO₂ manifested cognitive sequelae, but our study was underpowered to demonstrate that HBO₂ reduced cognitive sequelae in patients with longer CO exposures. However, patients with longer CO exposures should be treated with HBO₂, since their risk for cognitive sequelae is high.

The magnitude of neuropsychological impairments in patients with cognitive sequelae is substantial and not different between patients treated with or without HBO₂. The severity of the cognitive impairments underscores the importance for HBO₂ to reduce the probability of cognitive sequelae. Possible beneficial mechanisms for HBO₂ in CO poisoning include prevention of inflammation (28), reduced lipid peroxidation (29), and preservation of adenosine triphosphate function (30). It is conceivable that alternatives to HBO₂ could be developed or tried that might prevent some of these pathophysiologic processes, such as brain inflammation.

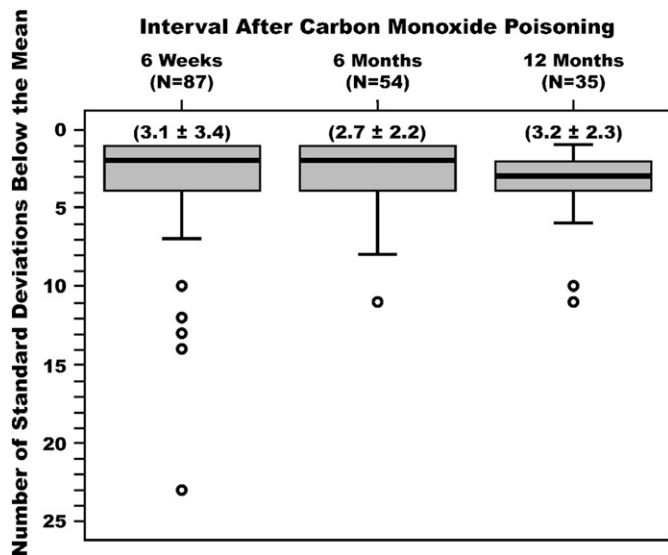


Figure 1. Magnitude of cognitive dysfunction. The magnitude of cognitive dysfunction is shown at 6 weeks, 6 months, and 12 months after acute CO poisoning in those patients with cognitive sequelae. The y-axis represents the number of standard deviations our patients scored below the mean of demographically compared normal population controls. The number of patients at each time are depicted as N = no. The mean ± SD values are also depicted on the figure. The shaded areas represent the 25th to 75th interquartile ranges. The end of the whisker is the maximum or minimum value that is not an outlier. Outliers are denoted by the open circles.

In patients 36 years or older, regardless of loss of consciousness, or initial COHb, four patients would need to be treated with HBO₂ to prevent one case of 6-week cognitive sequelae. There appear to be 40,000 to 50,000 Emergency Department visits annually in the United States due to CO poisoning (31, 32). Of this number of patients, approximately half would be 36 years or older. Therefore, without HBO₂, we estimate there would be at least 10,000 new cases of cognitive sequelae per year in the United States due to CO poisoning and HBO₂ should reduce the number who develop cognitive sequelae by 50% (1).

The subgroup analyses from our randomized trial suggest HBO₂ reduces cognitive sequelae in poisoned patients with loss of consciousness, in agreement with others (5–7). This observation is supported by animal studies indicating that loss of consciousness is required for brain lipid peroxidation-induced injury (33), which is reduced by HBO₂. However, multivariable logistic regression found loss of consciousness and loss of consciousness duration were not risk factors for cognitive sequelae. The anesthetic properties of CO (34) may explain why loss of consciousness may not be a risk factor for cognitive sequelae. Therefore, brain injury may be due to hypoxia in some poisoned patients, with or without loss of consciousness, and not all loss of consciousness may be attributable solely to brain hypoxia.

The subgroup analyses from our randomized trial suggest that HBO₂ reduces cognitive sequelae in patients with higher COHb levels. In our larger study, the initial and estimated COHb levels when CO exposures ended were not risk factors for cognitive sequelae, in agreement with other investigators (35). The COHb level may not be associated with mechanisms of injury such as lipid peroxidation (36), oxidative stress from neutrophil activation (37), immune-mediated damage (38), or premature apoptosis (39). Nevertheless, the initial COHb level is associated with putamen volume loss, but not cognitive

TABLE 4. UNIVARIATE ANALYSES OF POTENTIAL RISK FACTORS FOR COGNITIVE SEQUELAE IN 163 PATIENTS NOT TREATED WITH HBO₂ AFTER CO POISONING

Factors Considered as Potential Risks	Patients with Cognitive Sequelae (no./total no.) (%)	P Value
Age*		
< 36 yr	28/89 (32)	0.003
≥ 36 yr	41/74 (55)	
English speaking		
No	4/8 (50)	0.72
Yes	65/155 (42)	
Suicide attempt		
No	59/137 (43)	0.83
Yes	10/26 (39)	
Interval of exposure to CO*		
< 24 h	42/117 (36)	0.01
≥ 24 h	27/46 (59)	
Intermittent CO exposure†		
No	44/120 (37)	0.02
Yes	25/43 (58)	
Initial difficulties with memory		
No	39/104 (38)	0.04
Yes	24/42 (57)	
Loss of consciousness		
No	37/90 (41)	0.75
Yes	32/73 (44)	
Duration of loss of consciousness		
None	37/90 (41)	0.88
< 60 min	21/51 (41)	
≥ 60 min	10/21 (48)	
Initial COHb level*		
< 25%	40/99 (40)	0.73
≥ 25%	22/50 (44)	
Initial base excess*		
< -2 mmole/L	16/35 (46)	0.40
≥ -2 mmole/L	27/76 (36)	
Method of oxygen therapy delivery‡		
None	9/17 (53)	0.44
Simple mask or nasal cannula	5/16 (31)	
High-flow reservoir through a face mask that prevented rebreathing or by endotracheal tube	55/130 (42)	

Because of rounding, not all percentages total 100.

* Characteristic was initially analyzed as a continuous factor. The factor was converted and used as a categorical factor.

† Forty-one of 46 patients (89%) with CO exposure interval 24 h or longer had intermittent CO exposures. Two of 117 patients (2%) with CO exposure interval less than 24 h experienced intermittent CO exposures. Due to the strong statistical association between these two factors, we excluded intermittent exposure from further analyses.

‡ Refers to prime method of oxygen delivery, whether pre-hospital or hospital.

dysfunction (40), and for that reason patients with high COHb levels may benefit from HBO₂.

From our randomized controlled trial, initial cerebellar dysfunction was associated with 6-week cognitive sequelae (OR, 5.71) (1). Therefore, one could reason that poisoned patients with cerebellar dysfunction should receive HBO₂. However, even in patients with initial normal cerebellar function, HBO₂ reduced 6-week cognitive sequelae (P = 0.05) (1), so the presence of cerebellar dysfunction should not be used as the sole criteria for HBO₂. We did not have cerebellar examination results from the majority of patients from nonrandomized trials, so we did not include this factor in our analyses.

We cannot specify the interval from cessation of CO poisoning to HBO₂ that would convey reduced cognitive sequelae. Over 60% of patients in our randomized clinical trial (1) were treated with HBO₂ in less than 6 hours from poisoning, so our data is underpowered to determine if treatment with HBO₂ beyond 6 hours will also reduce cognitive sequelae.

The lack of association between initial symptoms and cognitive sequelae is an important finding. It appears that CO poisoning may initiate a cascade of pathophysiological process in the brain (38), which may lead to cognitive sequelae, yet these processes are not necessarily linked to the physical expression at the time of poisoning.

Contrary to expectation (36), for patients not treated with HBO₂, the time from CO removal to supplemental oxygen, the concentration of inhaled oxygen, or the duration of oxygen therapy were not associated with cognitive sequelae. Since oxygen is inexpensive, readily available, and probably does not worsen outcomes, we endorse the administration of 100% normobaric oxygen to patients with acute CO poisoning pending HBO₂. However, clinicians need to be aware that HBO₂, not necessarily 100% normobaric oxygen, reduces cognitive sequelae.

It is important to reiterate that the results we found are derived from patients enrolled in a randomized trial (1) and from poisoned patients not treated with HBO₂, but followed similarly. Inferences may be strengthened by including both patients from randomized trials and those from nonrandomized trials. In addition, the inclusion of patients from nonrandomized trials makes results more generalizable. All patients enrolled in our prior study (1) and the present study had symptomatic CO poisoning. Almost half the patients had an interval of unconsciousness and the initial mean COHb level was greater than 20%, with an estimated COHb level when poisoning stopped of 35%. In a study conducted in France, one of three patients with apparent milder poisoning appear to have persistent neurologic symptoms 1 month after poisoning (35). Comparisons of this study to ours is difficult, since they did not conduct standardized cognitive assessments and HBO₂ dosing was different (35).

Medical decision-making regarding HBO₂ for patients with acute CO poisoning needs to be balanced by side effects of HBO₂ and transport risk. The incidence of side effects and complications of HBO₂ is low (41). The most common side effect of hyperbaric pressurization is middle ear pressure equalization difficulties, which occur in approximately 2% of patients (41). The risk of seizures in large series of HBO₂-treated patients is approximately 0.02%. In patients with CO poisoning, the seizure rate ranged from 0.3 to 2.5%, without residua (41). With dedicated, experienced transport teams, risk of transport is extremely low (42). There were no transport-related mishaps or events in our randomized trial of HBO₂ for CO poisoning (43).

Our findings support that HBO₂ reduces cognitive sequelae in poisoned patients that are older or have longer exposures to CO. In addition, we agree with consensus opinion that mirrors our subgroup data: that HBO₂ is indicated for patients with loss of consciousness or higher carboxyhemoglobin levels.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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