Central nervous system oxygen toxicity during hyperbaric treatment of patients with carbon monoxide poisoning

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Hampson NB, Simonson SG, Kramer CC, Piantadosi CA. Central nervous system oxygen toxicity during hyperbaric treatment of patients with carbon monoxide poisoning. Undersea Hyperbaric Med 1996; 23(4):215–219.—Hyperbaric oxygen (HBO_2) is associated with a recognized risk for clinical central nervous system (CNS) toxicity. The risk for oxygen convulsions during routine hyperbaric treatment of most routine conditions is extremely low. Previous observations have suggested that the incidence of CNS toxicity during HBO_2 treatment for carbon monoxide (CO) poisoning may be increased, both because of CNS injury caused by the poisoning and because higher treatment pressures are often utilized for this condition. This study reviews data from 900 CO-poisoned patients treated with HBO_2 at Virginia Mason and Duke University Medical Centers from 1987 to 1996. One-third of the patient population was treated at each of the three HBO_2 treatment pressures most commonly utilized for CO intoxication in North American multiplace chambers. Patient characteristics were similar in all groups. Among the 300 consecutive patients treated at each pressure, there was one seizure at 2.45 atm abs (0.3%), nine seizures at 2.80 atm abs (2.0%), and six seizures at 3.00 atm abs. This difference is statistically significant ($P = 0.032$; Fisher's Exact Test). The potential difference in seizure risk should be considered when selecting the HBO_2 treatment pressure for CO poisoning.

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Central nervous system (CNS) oxygen toxicity, as manifest by clinically apparent seizure activity, is a recognized side effect of hyperbaric oxygen (HBO_2) therapy (1). Reports of large series of patients receiving HBO_2 therapy for miscellaneous routine conditions quote an incidence of CNS oxygen toxicity of approximately 1 in 10,000 hyperbaric treatments performed at 2.0 to 3.0 atm abs (2,3). In addition to seizures induced by O_2, convulsive activity may also result from the underlying condition prompting HBO_2 treatment. Examples of this include decompression illness and carbon monoxide (CO) poisoning, both of which may be associated with seizures due to cerebral ischemia or hypoxia (4,5).

Data from a 10-yr experience published recently suggested that the incidence of CNS O_2 toxicity during HBO_2 treatment of CO-poisoned patients may be higher than that reported among those treated for non-emergent conditions (6). The present study was performed to further evaluate that possibility and to investigate whether or not the incidence of CNS O_2 toxicity relates to the hyperbaric treatment pressure utilized.

METHODS

Medical charts and hyperbaric treatment records of consecutive patients treated with HBO_2 for CO poisoning at Virginia Mason Medical Center (VMMC) from December 1987 to November 1995 and at Duke University Medical Center (DUMC) from December 1988 to January 1996 were reviewed. Data were collected regarding patient demographics and clinical condition, details of the poisoning incident, and complications of hyperbaric treatment. An episode of CNS O_2 toxicity was defined as clinically apparent seizure activity at any time during the hyperbaric treatment.

Before February 1992, patients at VMMC were treated for CO intoxication with a hyperbaric protocol that administered two or four 23-min 100% O_2 breathing periods at 2.80 atm abs. Patients treated after that date were managed per the United States Air Force (USAF) CO protocol, involving the administration of two 23-min O_2 periods at 3.00 atm abs, followed by two additional 25-min O_2 periods at 2.00 atm abs (7). Patients treated at DUMC received 90 continuous minutes of 100% O_2 at 2.36 or 2.45 atm abs (pressure for this group will referred to as "2.45" hereafter for simplicity).

Data were analyzed using SAS statistical software (SAS Institute, Cary, NC). The primary outcome variable was the incidence of seizures at the three treatment pressures. This

was analyzed by Fisher's exact test with a P value less than 0.05 accepted as significant. Analysis of additional risk factors possibly impacting the incidence of seizures was performed for six variables including age, sex, carboxyhemoglobin (COHb) level, incidence of loss of consciousness (LOC), suicidal intent of exposure, and the requirement for mechanical ventilation during HBO_2. A simple Bonforoni correction of the P value accepted as significant was used for these analyses. Continuous variables were analyzed by analysis of variance or Students' t test for normally distributed variables or by the Kruskal-Wallis or Wilcoxon test if the data were not normally distributed. Categorical variables were evaluated by chi-square analysis.

RESULTS

Nine hundred CO-poisoned patients were studied; 600 at VMMC and 300 at DUMC. Half of those from VMMC were treated before February 1992. As such, the entire study population was divided into three groups of 300 patients treated at 2.45, 2.80, and 3.00 atm abs, respectively. Among those treated at 2.80 atm abs, 165 were administered two 23-min O_2 periods at pressure, while 135 received four periods.

Patient demographics are detailed in Table 1. For the entire population, average age was 34 ± 9 yr (mean ± SD), 67% were male, 50% experienced loss of consciousness with the poisoning, and average COHb level was 24.0 ± 11.4%. There were no significant differences with regard to age, sex, incidence of LOC, or requirement for mechanical ventilation among the groups of patients treated at each of the three pressures. Suicidal intent was highest in the 3.00 atm abs group and lowest in the 2.45 atm abs group. COHb level was statistically different between the three groups ($P = 0.001$; Kruskal-Wallis analysis). Carboxyhemoglobin levels were minimally higher in those patients experiencing LOC as compared to those without LOC (24.6 ± 12.9% vs. 22.8 ± 9.7%). Sources of CO exposure for the total population and each treatment subgroup are detailed in Table 2.

Seizure activity occurred during HBO_2 in 16 of the 900 patients (1.8%) (Table 3). Seizures developed in 1 of 300 patients treated at 2.45 atm abs (0.3%), 9 of 300 patients treated at 2.80 atm abs (3.0%), and 6 of 300 patients treated at 3.00 atm abs (2.0%). The difference in incidence of CNS O_2 toxicity between groups was statistically significant ($P = 0.032$; Fisher's Exact Test, two-tailed). All seizures occurred during the initial HBO_2 treatment of an episode of CO poisoning. Duration of 100% O_2 breathing at hyperbaric pressure before development of seizure activity is detailed in Table 4. There was no difference in the time to seizures between the 2.80 and 3.00 atm abs groups ($P = 0.8$).

In all 16 cases, seizures were initially managed by switching the patients from 100% O_2 to air breathing. Diazepam was also administered to six of the patients. All seizures stopped within minutes after removal from O_2 breathing, whether anticonvulsant medication was given or not. Hyperbaric treatment was aborted following the initial seizure in seven cases and continued after 15 min of air breathing in nine cases. One patient experienced a second seizure after HBO_2 administration was resumed, prompting abortion of the treatment. Among the eight others, seizure activity did not recur and the planned hyperbaric treatment was completed. No patient experiencing a seizure was offered a second HBO_2 treatment. No adverse sequellae are known to have resulted from the seizures.

Characteristics of patients with and without seizures are compared in Table 5. There were no significant differences

Table 1: Patient Characteristics

	All Patients $n = 900$	2.45 atm abs $n = 300$	2.80 atm abs $n = 300$	3.00 atm abs $n = 300$
Age, yr	34 ± 19	34 ± 19	33 ± 19	34 ± 17
Sex	67% M	66% M	79% M	65% M
Loss of consciousness	50%	52%	50%	47%
COHb level, %				
Mean ± SD	24.0 ± 11.4	26.6 ± 12.0	23.9 ± 11.5	21.4 ± 9.8
Range	0.0–72.3	0.2–68.6	0.0–72.3	0.1–60.0
Suicidal intent, %	24	18	23	32
Mechanically ventilated during HBO_2, %	15	17	13	14

Table 2: Sources of Carbon Monoxide Exposure

	All Patients $n = 900$	2.45 atm abs $n = 300$	2.80 atm abs $n = 300$	3.00 atm abs $n = 300$
Motor vehicle, %	38	33	40	42
Fire, %	10	14	10	7
Indoor charcoal, %	9	2	6	19
Furnace, %	8	15	7	1
Electrical generator, %	7	9	4	7
Boat, %	5	0	6	8
Miscellaneous, %	23	27	27	16

Table 3: Incidence of CNS Oxygen Toxicity During HBO_2 Treatment

	All Patients $n = 900$	2.45 atm abs $n = 300$	2.80 atm abs $n = 300$	3.00 atm abs $n = 300$
Number of patients with seizures	16 (1.8%)	1 (0.3%)	9 (3.0%)	6 (2.0%)

Table 4: Duration of 100% Oxygen Breathing Before Development of Seizure Activity

Treatment Pressure	Oxygen Time, min
2.45 atm abs	45
2.80 atm abs	15, 16, 18, 22, 23, 44, 46, 58, 69
3.00 atm abs	18, 23, 32, 35, 40, 46

in the selected characteristics. Among the 16 patients developing seizures, 10 were taking medications before CO poisoning and/or administered medications as part of their emergency care. Medications taken by patients experiencing CNS O_2 toxicity are listed in Table 6. Medication history was not tabulated in the 884 patients who did not experience seizures. None of the patients experiencing seizures during hyperbaric treatment had a recognized pre-existing seizure disorder.

DISCUSSION

Carbon monoxide poisoning is extremely common in the United States (8). Hyperbaric oxygen is frequently utilized as treatment for the most severely poisoned subset of intoxicated patients. In 1992, approximately 2,600 CO-poisoned patients were treated with HBO_2 in North America; 1,200 in monoplace chambers and 1,400 in multiplace chambers (9). Such patients are treated in the belief that the benefit from HBO_2 therapy for their condition outweighs the risks associated with hyperbaric treatment (10).

A wide variety of hyperbaric treatment protocols are utilized for HBO_2 therapy of CO poisoning. A recent survey of North American multiplace hyperbaric treatment facilities found that 18 different treatment protocols are utilized for primary treatment of the CO-poisoned patient (11). Among these different protocols, 3 apply a maximum treatment pressure of 3.0 atm abs, 13 protocols 2.8 atm abs, and 2 protocols 2.4–2.5 atm abs. When one multiplies the minutes of O_2 breathing by atm abs pressure, it is found that the O_2 dose delivered by the protocols differs by a factor of more than 3-fold.

During the year studied in that report (11), 28% of patients were treated at facilities utilizing 3.0 atm abs, 55% at facilities utilizing 2.8 atm abs, and 17% at facilities utilizing 2.4–2.5 atm abs. Although this might suggest a consensus for treatment at 2.8 atm abs, it should be realized that this slight majority of patients was divided among 13 different protocols utilizing that treatment pressure. The protocol most frequently utilized is the USAF CO protocol, applied by 33% of multiplace facilities and used to treat 15% of patients managed in multiplace hyperbaric chambers in 1990.

No comparative studies exist that compare clinical outcomes of CO-poisoned patients treated at different pressures. Comparison of results from different centers is complicated because selection criteria applied for hyper-

Table 5: Characteristics of Patients With and Without CNS Oxygen Toxicity

	Patients With Seizure, $n = 16$	Patients Without Seizure, $n = 884$	P Value
Age, yr	36 ± 17	33 ± 19	0.99
Sex	81% M	67% M	0.29
Loss of consciousness, %	56	50	0.62
COHb level, %			
Mean ± SD	28.0 ± 15.7	23.9 ± 11.2	0.95
Range	3.4–72.3	0.0–68.6	
Suicidal intent, %	44	24	0.08
Mechanically ventilated during HBO_2, %	25	14	0.27
Most common CO source	motor vehicle, 50%	motor vehicle, 38%	

Table 6: Medications Taken by 2 or More of the 16 Patients Manifesting CNS Oxygen Toxicity

Medication	Number of Patients (%)
Acetaminophen	4 (25)
Benzodiazepine	4
Narcotic	4
Skeletal muscle relaxant	4
Inhaled bronchodilator	3 (19)
Theophylline	2 (12)
Corticosteroid	2
Phenothiozine	2

baric treatment vary widely among hyperbaric medical directors (9) and published reports frequently do not stratify patient outcome relative to severity of poisoning. The paucity of information regarding treatment pressure is reflected in the recommendation of the Hyperbaric Oxygen Committee of the Undersea and Hyperbaric Medical Society (UHMS), which suggests only that a treatment pressure from 2.4 to 3.0 atm abs be used (10).

In addition to clinical outcome following treatment at different pressures, side effects of treatment should be considered when selecting an HBO_2 protocol. Limited published data are available in this regard, as well. One available report noted that 14 of 297 (5%) patients with CO poisoning treated at 3.0 atm abs experienced focal or generalized seizure activity (6). Data are unavailable for lower treatment pressures.

The present study demonstrates an overall 1.8% incidence of CNS O_2 toxicity among CO-poisoned patients treated at the range of pressures utilized in North American multiplace hyperbaric chambers and recommended by the UHMS. This rate is significantly higher than the 0.01% reported during HBO_2 treatment of non-emergent patients (1,2). Furthermore, the difference in incidence seen in our study (0.3% at 2.45 atm abs, 3.0% at 2.80 atm abs, 2.0% at 3.00 atm abs) was statistically significant with regard to maximum treatment pressure.

While arterial blood gas measurements during HBO_2 administration are not available for the entire patient population, gas exchange efficiency should have been similar among the group of patients who experienced seizures and those who did not. There was no statistical difference in either incidence of loss of consciousness or requirement for mechanical ventilation between the groups, factors which might be markers of lung injury and associated impairment of pulmonary gas exchange. It is likely, therefore, that the statistically significant association of seizure activity with hyperbaric treatment pressure is due to the partial pressure of O_2 administered.

It is well known that CO poisoning itself can induce seizure activity (5). A seizure rate of 1–3% before HBO_2 therapy has been reported among patients poisoned severely enough to warrant referral for hyperbaric treatment (6,12). The episodes of CNS O_2 toxicity in the current study cannot be ascribed to either CO intoxication alone or differences in severity of poisoning among the three treatment groups. All patient characteristics were similar, with the exception of the average COHb level which was slightly higher in the group treated at 2.45 atm abs. It is doubtful whether the difference in COHb levels

between the three treatment groups is clinically meaningful, but one would expect the rate of CNS O_2 toxicity to be greater among patients with higher COHb levels. This is opposite to the relationship seen among our patient population. In addition, the statistically greater number of seizures at higher pressure indicates that O_2 itself is playing a causative role. None of the patients developing seizures during HBO_2 were known to have done so before treatment.

The slightly higher incidence of seizures at 2.80 atm abs as compared to 3.00 atm abs may be in part explained by differences in the hyperbaric protocols (*see* Methods). Patients treated at 2.80 atm abs received 46 or 92 min of 100% O_2, whereas those treated at 3.00 atm abs received only 46 min of O_2 at that pressure. As two seizures in the 2.80 atm abs group did not occur until after 46 min, it is likely that additional incidents of CNS O_2 toxicity would have occurred in the 3.00 atm abs group if O_2 administration at maximum pressure had been longer.

As detailed in Table 5, no analyzed characteristic was statistically more common among patients experiencing seizures during HBO_2 than among those who did not. There was a nonsignificant trend toward increased seizure frequency among those poisoned with CO with suicidal intent. One possible explanation for this could be the simultaneous ingestion of additional CNS-toxic substances. Alternatively, brain injury may be more severe among suicidal patients due to longer CO exposure or greater delay to treatment.

We conclude that O_2 convulsions during HBO_2 therapy are more common among CO-poisoned patients than the general hyperbaric patient population. Furthermore, the risk for O_2 convulsions is related to the partial pressure of O_2 utilized for treatment. In the absence of data defining an optimum treatment pressure, CNS O_2 toxicity should be considered when selecting a HBO_2 protocol for treatment of the CO-poisoned patient. Since O_2 convulsions are undesirable in patients with possible neurologic injuries, studies need to be conducted to examine neurologic outcome in patients treated at different pressures vs. risk of seizures. If benefit related to increased pressure cannot be demonstrated, patients with CO poisoning should be treated at the lowest effective pressure to avoid O_2 convulsions.

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