Delayed Neuropsychologic Sequelae After Carbon Monoxide Poisoning: Prevention by Treatment With Hyperbaric Oxygen

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See related editorial, p 535.

Study objective: Carbon monoxide (CO) poisoning is a major clinical problem. The risk of morbidity and the most effective treatment have not been clearly established. We measured the incidence of delayed neurologic sequelae (DNS) in a group of patients acutely poisoned with CO and tested the null hypothesis that the incidence would not be affected by treatment with hyperbaric oxygen (HBO).

Design: We conducted a prospective, randomized study in patients with mild to moderate CO poisoning who presented within 6 hours. Patients had no history of loss of consciousness or cardiac instability.

Interventions: The incidence of DNS was compared between groups treated with ambient pressure 100% oxygen or HBO (2.8 ATA for 30 minutes followed by 2.0 ATA oxygen for 90 minutes). DNS were defined as development of new symptoms after oxygen treatment plus deterioration on one or more subtests of a standardized neuropsychologic screening battery.

Results: In 7 of 30 patients (23%), DNS developed after treatment with ambient-pressure oxygen, whereas no sequelae developed in 30 patients after HBO treatment ($P<.05$). DNS occurred 6±1 (mean±SE) days after poisoning and persisted 41±8 days. At follow-up 4 weeks after poisoning, patients who had been treated with ambient pressure oxygen and had not sustained DNS exhibited a worse mean score on one subtest, Trail Making, compared with the group treated with HBO and with a control group matched according to age and education level. There were no differences in scores between the control group and the hyperbaric oxygen group.

Conclusion: DNS after CO poisoning cannot be predicted on the basis of a patient's clinical history or CO level. HBO treatment decreased the incidence of DNS after CO poisoning.

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INTRODUCTION

Carbon monoxide (CO) is a major environmental toxicant that frequently causes death or neurologic morbidity.[1] Since the pioneering studies of Haldane[2], the principal cause of acute mortality has been attributed to hypoxic stress due to formation of carboxyhemoglobin (COHb) with an associated decrease in blood oxyhemoglobin. However, the pathophysiology of delayed neuropsychologic sequelae (DNS) cannot be explained simply by an acute hypoxic stress; symptoms appear after the COHb level has fallen. Symptoms of DNS typically develop after an interval of two to 40 days. Sequelae may include headache, difficulty concentrating, lethargy, emotional lability, amnestic syndromes, dementia, psychosis, parkinsonism, chorea, apraxia, agnosia, peripheral neuropathy, and urinary incontinence.3 The risk of an adverse outcome of CO poisoning has not been predictable on the basis of clinical history or laboratory testing. Published clinical series of 50 or more "seriously poisoned" patients report that mortality varies from less than 1% to 34%; neurological morbidity has varied from less than 1% to 47%.4-17

Supplemental oxygen, usually administered through a nonrebreather mask, is the standard treatment for acute CO poisoning. Hyperbaric oxygen (HBO) has been recommended for serious poisonings and for patients with high COHb levels on the basis of results from retrospective and nonrandomized trials.[13-16] In 1989 a prospective, randomized trial was reported comparing normobaric and HBO treatment for patients who had not lost consciousness and, hence, in patients without severe poisoning.[17] A surprisingly high incidence of neuropsychologic sequelae, more than 40%, was found in both treatment groups.[17]

Concerns with this study include the absence of an objective or quantitative evaluation of cortical function. DNS was diagnosed when patients reported any of a variety of complaints on a self-assessment questionnaire that was mailed 1 month after poisoning. Moreover, oxygen treatment did not begin until more than 6 hours after poisoning in approximately half of the cases. In 1969, Goulon et al[13] suggested in a retrospective study of patients evaluated by direct physical examination that HBO was effective only if begun within 6 hours of the end of exposure.

The aims of this study were to assess the incidence of DNS after CO poisoning and to determine whether the incidence of DNS was different between groups treated with ambient pressure oxygen or HBO.

MATERIALS AND METHODS

This study was a prospective, randomized, nonblinded comparative trial of HBO and normobaric oxygen therapy. Patients were referred from emergency departments in our region. Informed consent involved having the patient read or be read a form outlining the two possible oxygen treatments and clearly stating that neither treatment has been proved effective in preventing neurological sequelae following CO poisoning. The study was approved by our institutional review board.

Patients were randomly assigned to one of two treatment arms. Neither the patients nor investigators were blinded to treatment: HBO at a pressure of 2.8 ATA for 30 minutes, followed by 2.0 ATA for 90 minutes; or normobaric treatment with 100% oxygen through a nonrebreather face mask until all symptoms resolved.

Table 1.
Characteristics of study population.

Characteristics	Ambient-Pressure Oxygen	HBO
No. of patients	32 (14 F, 18 M)	33 (17 F, 16 M)
COHb (%)	20.0±1.6	24.6±1.4
Age (yr)	39.0±3.4	35.0±2.9
Education (yr)*	−.2±.6	−.1±.6
Medical history		
Hypertension/cardiovascular disease	4	2
Pulmonary disease	2	1
Neurologic disorders	0	1
Near syncope	3	6
Signs/symptoms in ED		
Headache	25	20
Nausea/vomiting	10	10
Lethargy	10	12
Confusion	5	5
Obtundation	3	4
Time elapsed until ambient-pressure oxygen treatment started (hr)	1.1±.3	1.0±.2†
Duration of oxygen therapy (hr)	4.2±3	2.0±.2

*0, High school graduate.
†Patients received ambient-pressure oxygen until HBO was initiated.

Three inclusion criteria were used: history of acute exposure to combustion products, an increased COHb level that could not be explained by a smoking history, and the presence of symptoms consistent with CO poisoning (Table 1). Three eligible patients declined to participate. Exclusion criteria included history of unconsciousness and cardiac compromise diagnosed on the basis of chest pain or ischemic changes on ECG.

In addition to a standard physical examination, the blood COHb content and a chest radiograph were obtained for each patient. HBO treatments were carried out in the multiplace chambers at the Institute for Environmental Medicine, University of Pennsylvania.

In all cases, HBO treatment began within six hours after a patient was removed from the CO source. Symptoms in this group usually resolved during the second hour of HBO treatment, and in all patients symptoms had resolved by the end of the 2-hour treatment. No adverse effects resulted from hyperbaric treatment.

After completion of normobaric oxygen or HBO treatment, each patient was administered a neuropsychologic screening battery consisting of six subtests.[18] The subtests included General Orientation, to establish rapport and assess recall of personal facts; Digit Span, a test of short-term memory assessed as the ability to remember and recite a series of digits; Trail Making, an assessment of temporospacial orientation and visual discrimination assessed on the basis of a patient's ability to connect a pattern of dots; Digit Symbol, a timed test of visual discrimination and visual-motor coordination in which patients transcribe numbers to symbols; Aphasia Screen, a series of tests to evaluate language and praxic functions; and Block Design, a timed test that evaluates visual-spacial functioning by construction of geometric designs with red and white blocks.

Testing was usually carried out in a quiet area adjacent to the ED or adjacent to the hyperbaric chambers. Our goal was to obtain initial test scores promptly after treatment and at a time when patients felt well. In instances when patients stated they were too fatigued to perform tests because treatment was completed late at night, testing was performed in the patient's home within 12 hours. These tests' results were defined as a patient's "baseline," and all follow-up test scores were compared with this result. DNS were defined as a recurrence of original symptoms or development of new symptoms considered to be typical of the DNS syndrome[3], plus a deterioration in one or more subtest scores on the neuropsychometric screening battery.

Patients were instructed to contact a staff member, who was on call 24 hours a day, if they noted any abnormal symptoms. The patient was then examined at the clinic or, in most cases, in the home. The physical examination was performed on these patients, and the neuropsychologic test was repeated. To ascertain whether some patients did not report symptoms, all patients were interviewed within 1 week of treatment. None of these patients reported symptoms. All asymptomatic patients underwent formal neuropsychologic testing 3 to 4 weeks after CO poisoning. Patients were also interviewed by telephone at three months to confirm that new symptoms had not occurred. Seven patients were tested after they reported new symptoms consistent with DNS. Three patients refused follow-up neuropsychologic examinations after they felt well. In the other four, the neuropsychologic tests were repeated at intervals of 2 to 3 weeks until scores returned to baseline. Normalization of scores coincided with patients becoming clinically asymptomatic. No specific treatment of patients with DNS was undertaken.

Repeated neuropsychologic screening has been shown to improve scores.[18] To assess the influence of practice in our patients, we studied a control population of eight individuals with similar mean age and education after completing the studies on CO-poisoned patients. The control group included four women and four men; their mean age was 40.4±7 years, and their education level was .1±2.0 years less than a complete high school education.

The incidences of DNS in groups treated with ambient-pressure oxygen and HBO was compared by means of a two-tailed χ^2 test. Comparisons of subtest scores between groups treated with ambient-pressure oxygen or hyperbaric oxygen and controls were made with ANOVA followed by Scheffé's test.[19] For all statistical analyses, a P value of less than .05 was considered significant.

Table 2.
Initial neuropsychologic subtest scores obtained after oxygen treatment (mean±SE).

Group	N	General Orientation	Digit Span	Trail Making	Digit Symbol	Aphasia Screen	Block Design
Ambient-pressure oxygen	30	0±0	7.3±.2	70±3	52±3	0±0	37±2
HBO	30	0±0	7.0±.2	73±6	53±3	0±0	41±2

RESULTS

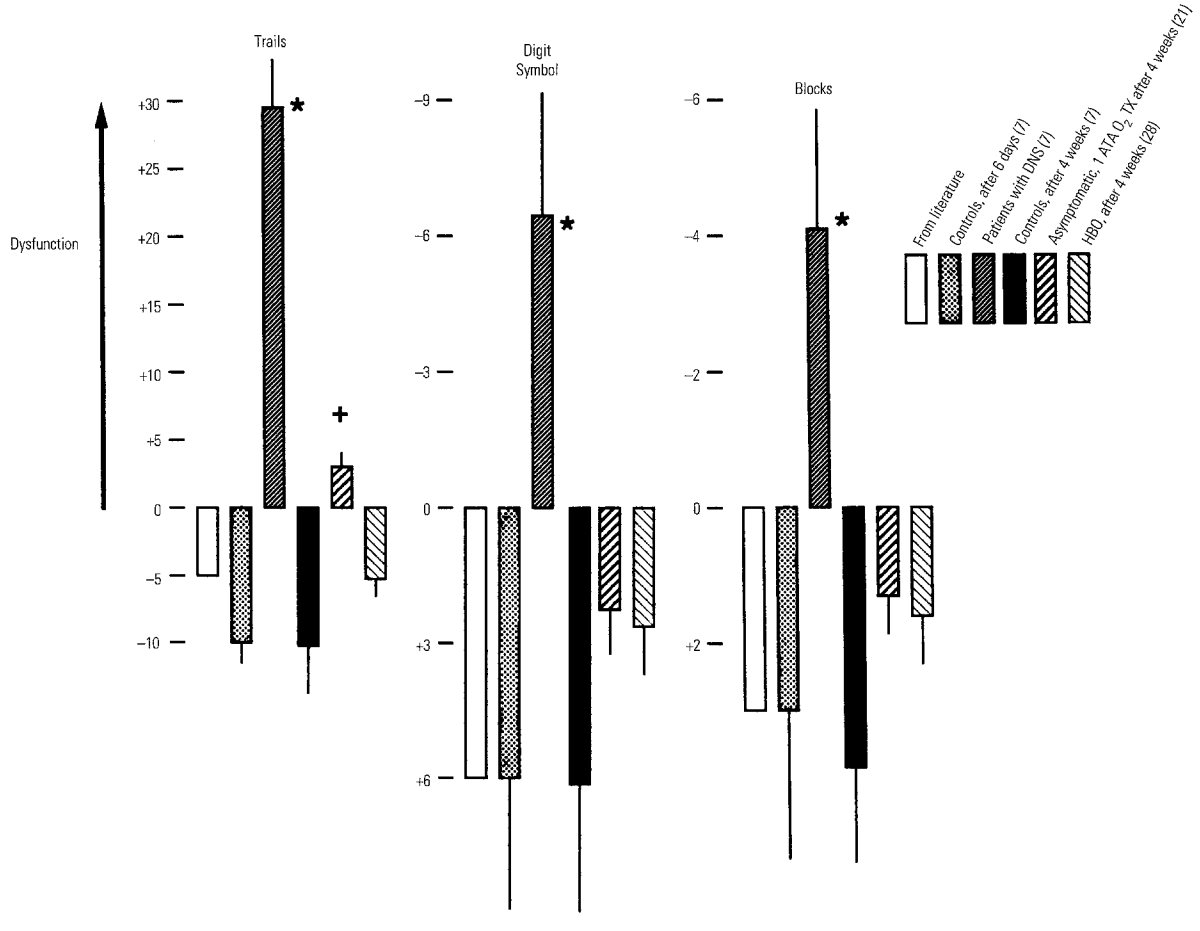
Between September 18, 1989 and December 20, 1993, 65 patients were enrolled; 32 patients were treated with ambient-pressure oxygen, and 33 patients received HBO.

Two patients in the ambient-pressure group and three in the HBO group were lost to follow-up. Two patients in each treatment group refused formal neuropsychologic retesting but denied symptoms of DNS during telephone interviews conducted over the next 3 months.

Patients in the two treatment groups were similar, and their signs and symptoms in the ED were quite similar (Table 1). Neurologic status after oxygen treatment was not discernibly different between groups, and scores on the initial neuropsychologic test were not statistically different (Table 2).

In eight patients in the ambient-pressure group, symptoms consistent with DNS developed. Seven of these patients also had deterioration in at least one subtest category and were considered to have DNS (Table 3). One patient complained of headache and difficulty with concentration on days 3 to 14 after treatment. His test scores were normal, however, so he was not included as a case of DNS. No new symptoms occurred among the patients in the hyperbaric oxygen group ($P<.05$). The 95% CI on the difference between the proportion of patients in whom DNS developed in the two groups (23% versus 0%) was 8.2% to 38.4%.

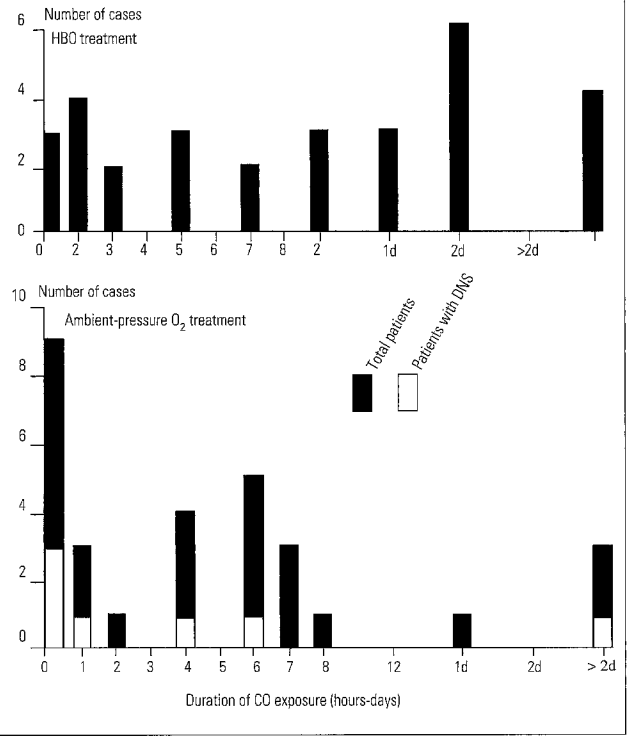
Figure 1.
Mean changes in psychometric test scores. Scores from the literature reflect the improvements achieved by practice in a control population.[18] Other groups are as described in the text.



*Significantly different from the 6-day control group;
+Significantly different from the group treated with hyperbaric oxygen and the control group tested at 4 weeks.
Values are the mean change +SE in scores compared with scores on corresponding subtests when patients were asymptomatic after treatment with oxygen.

Deteriorations in the DNS group scores occurred in three subtests: Trail Making, Digit Symbol, and Block Design. The mean changes in scores were significantly different from those of a matched control group (Figure 1). No differences were found in subtests on General Orientation, Digit Span recitals, or Aphasia Screening (results not shown). The test scores in control subjects at the 6-day and 4-week evaluations showed improvements in comparison to the initial scores. These changes were attributed to familiarity and practice (Figure 1). The scores of patients treated with HBO and tested at 4 weeks showed a similar improvement over scores from the initial testing. Patients who were treated with ambient-pressure oxygen and remained asymptomatic were found at 4 weeks to have slight deterioration in their scores on the Trail Making subtest. This was significantly different from the improved scores seen in both the control group and the HBO group. The lack of improvement may reflect the presence of a subtle impairment of learning ability when these patients first took the psychometric test and hence a lack of familiarity on retesting. Scores on the other subtests in this treatment group were not significantly different from those of the control group.

Figure 2.
Duration of exposure to CO, estimated on the basis of a patient's history.



The mean age of the seven patients with DNS was 46 years, whereas for the remaining 23 patients in the ambient-pressure group in whom DNS did not develop the mean age was 37 years (Table 1). This difference was not statistically significant. There were no apparent differences in the clinical histories of the DNS patients. The mean time to oxygen treatment was 1.1 hour for both groups. Three patients who sustained CO poisoning due to smoke inhalation were randomized to the ambient-pressure oxygen group, and only one of these cases had DNS. The COHb level in patients who went on to exhibit DNS was 19%±4%, compared with 20%±2% in the other patients treated with ambient-pressure oxygen. The duration of exposure to CO may be a risk factor for DNS.[20-22] In our study, however, no pattern in duration of CO exposure was discernible between patients with DNS and others treated with ambient-pressure oxygen, or between the ambient-pressure oxygen and HBO groups (Figure 2).

DNS persisted for a mean of 41±8 days. Four of the seven patients were able to carry on with their normal daily activities despite their symptoms. Three patients had difficulties with daily activities, as reported by both themselves and by family members. Patient 2 found that she could not return to work between the day of DNS onset (day 3) until day 13 after exposure (Table 3). Patients 4 and 6 found that lethargy and inability to concentrate left them unable to carry on their normal daily activities. In patient 4, an intention tremor was experienced with the onset of DNS; this persisted for 3 weeks. No other abnormal physical findings were seen in the seven cases.

DISCUSSION

We found a 23% incidence of DNS, similar or slightly lower than those reported in several studies in which treatment did not include HBO.[9,13,16] HBO treatment was associated with significant reduction in the incidence of DNS in our study. This differs from Raphael et al.[17] Assuming that the questionnaire responses in that study did indeed reflect DNS, we believe the success of HBO treatment may require its administration within 6 hours after CO poisoning. Patients in the Raphael study[17] were randomized for treatment at a mean time of almost 6 hours. The mean time for the initiation of HBO treatment in our study was 2.0±.2 hours. The oxygen partial pressure may also be important. We used a peak pressure of 2.8 ATA, whereas others have used 2.0 ATA.[17]

Neither the COHb levels nor other aspects of the CO exposures were found to be different in patients in whom DNS developed. The mean COHb levels in our study were quite low in several patients in whom DNS developed. Several studies have demonstrated that the COHb level does not correlate with clinical findings or with prognosis.[5,10,11,15] Therefore our findings demonstrate again that the molecular mechanism for CO-mediated morbidity is unknown. In animals, low concentrations of CO can cause perivascular oxidative changes, possibly in part because of release by platelets of the free radical nitric oxide.[23,24] We speculate that this relatively subtle vascular insult may initiate pathologic changes that lead to DNS.

The mechanism of action for HBO therapy should also be investigated. In animals, oxidative stress in the brain occurs after CO poisoning because of leukocyte activation, and learning deficits have been documented in rats several days later.[25,26] HBO treatment has been shown to prevent leukocyte-mediated inflammatory changes in the brain and also prevents abnormalities in learning.[26,27] A mechanism for the effect of HBO is inhibition of leukocyte B_2 integrins, which mediate leukocyte-to-endothelial cell adhesion.[27] HBO also inhibits B_2 integrin–dependent adherence of human polymorphonuclear leukocytes.[28] Marginal inhibition was found after exposure to 2.0 ATA oxygen, and virtually complete inhibition occurred after exposure at 2.8 ATA oxygen for 45 minutes. These studies provide a possible mechanistic basis for the clinical benefit of HBO in CO poisoning.

We used a neuropsychologic screening test that provides a sensitive assessment of cerebral dysfunction.[18] This test was used to improve confidence in the diagnosis of DNS. A weakness of our study is the lack of blinding. We reduced bias by limiting the number of examiners and rigorously adhering to protocols when administering the neuropsychometric tests. A blinded study was not used because of the decompression risk posed by sham hyperbaric treatments. The incidence of DNS was unknown, and we were unwilling to accept any extra risk to patients resulting from sham treatment. Furthermore, during follow-up examinations, patients were likely to make comments about people or events associated with the oxygen treatment they received. This would have nullified blinding.

In large clinical series, approximately 50% to 75% of patients with DNS recover spontaneously over a period of 2 years.[10,11] Those who fail to recover often include patients suffering from more severe neurologic impairment such as parkinsonism, paralysis, or cortical blindness. Several of the patients in our study sustained moderate functional impairment due to DNS; all eventually recovered. We speculate that severe neurologic impairments did not occur because our study was conducted on relatively mildly poisoned patients. Before any systematic effort is made to treat mildly poisoned patients with HBO, however, we believe that additional studies are necessary. Questions that should be addressed include whether treating patients more than 6 hours after poisoning is effective and whether the benefits outweigh the costs of transportation and treatment.

CONCLUSION

Treatment with HBO reduced the incidence of DNS in our study population. The results also demonstrate that neither clinical history nor the COHb level predicts which patients may show DNS after CO poisoning.

Table 3.
Patients with DNS.

Patient No.	Age/ Sex	Admission COHb (%)	Time to Treatment (hr)	Duration of Treatment (hr)	Source of CO	Day of DNS Onset and Resolution	Symptoms
1	17/F	12	0.5	8	Furnace	8/31	Headache, fatigue, ataxia, difficulty concentrating
2	22/F	9	0.2	6	Automobile	3/25	Headache, malaise, difficulty concentrating
3	26/F	20	0.2	4	Furnace	10/33	Irritability, emotional lability, difficulty concentrating
4	49/F	7	0.5	4	Fire	3/76	Headache, dizziness, difficulty following conversations, tremor
5	63/M	14	0.5	6	Furnace	7/42	Headache, nausea/vomiting, dizziness
6	65/F	31	5	8	Furnace	9/77	Headache, confusion, fatigue
7	78/F	37	0.8	8.5	Automobile	2/42	Fatigue, malaise, difficulty concentrating

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