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HYPERBARIC OXYGEN FOR ACUTE CARBON MONOXIDE POISONING

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ABSTRACT

Background Patients with acute carbon monoxide poisoning commonly have cognitive sequelae. We conducted a double-blind, randomized trial to evaluate the effect of hyperbaric-oxygen treatment on such cognitive sequelae.

Methods We randomly assigned patients with symptomatic acute carbon monoxide poisoning in equal proportions to three chamber sessions within a 24-hour period, consisting of either three hyperbaric-oxygen treatments or one normobaric-oxygen treatment plus two sessions of exposure to normobaric room air. Oxygen treatments were administered from a high-flow reservoir through a face mask that prevented rebreathing or by endotracheal tube. Neuropsychological tests were administered immediately after chamber sessions 1 and 3, and 2 weeks, 6 weeks, 6 months, and 12 months after enrollment. The primary outcome was cognitive sequelae six weeks after carbon monoxide poisoning.

Results The trial was stopped after the third of four scheduled interim analyses, at which point there were 76 patients in each group. Cognitive sequelae at six weeks were less frequent in the hyperbaric-oxygen group (19 of 76 [25.0 percent]) than in the normobaric-oxygen group (35 of 76 [46.1 percent], P=0.007), even after adjustment for cerebellar dysfunction and for stratification variables (adjusted odds ratio, 0.45 [95 percent confidence interval, 0.22 to 0.92]; P=0.03). The presence of cerebellar dysfunction before treatment was associated with the occurrence of cognitive sequelae (odds ratio, 5.71 [95 percent confidence interval, 1.69 to 19.31]; P=0.005) and was more frequent in the normobaric-oxygen group (15 percent vs. 4 percent, P=0.03). Cognitive sequelae were less frequent in the hyperbaric-oxygen group at 12 months, according to the intention-to-treat analysis (P=0.04).

Conclusions Three hyperbaric-oxygen treatments within a 24-hour period appeared to reduce the risk of cognitive sequelae 6 weeks and 12 months after acute carbon monoxide poisoning. (N Engl J Med 2002; 347:1057-67.)

CARBON monoxide poisoning is a serious health problem[1,2] resulting in approximately 40,000 visits to the emergency department annually in the United States.[2,3] Unfavorable cognitive sequelae (problems with memory, attention or concentration, and affect) can occur immediately after exposure and persist or can be delayed, but they generally occur within 20 days after carbon monoxide poisoning.[1-6] Cognitive sequelae lasting one month[5,7-9] or more[2,4] appear to occur in 25 to 50 percent of patients with loss of consciousness or with carboxyhemoglobin levels greater than 25 percent.[2,7,8] The recommended treatment for acute carbon monoxide poisoning is 100 percent normobaric oxygen,[1,2,10,11] commonly delivered from a reservoir through a face mask that prevents rebreathing. Hyperbaric-oxygen therapy is often recommended for patients with acute carbon monoxide poisoning, especially if they have lost consciousness or have severe poisoning.[1,3,10,11]

Advantages of treatment with hyperbaric oxygen include increased dissolved-oxygen content in blood[10] and accelerated elimination of carbon monoxide.[11,12] Potential benefits of hyperbaric-oxygen treatment include prevention of lipid peroxidation in the brain[13] and preservation of ATP levels in tissue exposed to carbon monoxide.[2,3,11] Disadvantages of hyperbaric-oxygen therapy include risks associated with the transport of the patient to a treatment center, hyperoxic seizures,[14] and barotrauma.[3,10] It is difficult to establish the benefit–risk ratio of hyperbaric-oxygen treatment for the purposes of clinical decision making because

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the published results are conflicting.[1-3,5,6,8-10,15,16] We conducted a double-blind, randomized clinical trial to compare the rate of cognitive sequelae in patients with carbon monoxide poisoning treated with hyperbaric oxygen with the rate in those treated with normobaric oxygen.

METHODS

Study Patients

Emergency departments in Utah, Idaho, and Wyoming referred 98 percent of all patients with known carbon monoxide poisoning to LDS Hospital in Salt Lake City from November 1992 through February 1999. The institutional review board at LDS Hospital approved the study protocol. Written informed consent was obtained from patients or their surrogates before enrollment.

Patients were eligible for enrollment if they had a documented exposure to carbon monoxide (elevation of the carboxyhemoglobin level or the ambient carbon monoxide concentration) or an obvious exposure to carbon monoxide and if they had any of the following symptoms: loss of consciousness, confusion, headache, malaise, fatigue, forgetfulness, dizziness, visual disturbances, nausea, vomiting, cardiac ischemia, or metabolic acidosis (a calculated base excess lower than −2.0 mmol per liter or a lactate concentration higher than 2.5 mmol per liter). If the carboxyhemoglobin level was below 10 percent, the patient was eligible only if carbon monoxide poisoning was the only plausible diagnosis. Seven patients had carboxyhemoglobin levels lower than 10 percent but met the criteria for enrollment because they had an observed exposure to carbon monoxide, delays in the measurement of carboxyhemoglobin, and symptoms attributable only to carbon monoxide poisoning. Patients were excluded if more than 24 hours had elapsed since the exposure to carbon monoxide had ended (as in accepted practice[17]); if they were younger than 16 years of age; if they were moribund; if informed consent could not be obtained; or if they were pregnant.

Patients were randomly assigned to receive hyperbaric-oxygen therapy or normobaric-oxygen therapy with the use of blocked, stratified randomization with allocation determined by a list of computer-generated random numbers; treatment-group assignments were given to respiratory therapists in protected, sequentially numbered, sealed, opaque envelopes. The block size was six, and patients were stratified according to whether or not they had lost consciousness,[4,5,8] the interval between the end of the exposure to carbon monoxide and entry into the chamber (<6 hours or ≥6 hours),[5,8] and age (<40 years or ≥40 years).[4] We chose to assess the end point at six weeks in order to identify patients in whom delayed cognitive sequelae developed.[1,4-6]

Treatment Procedures

Referring physicians gave normobaric-oxygen therapy to patients with carbon monoxide poisoning. They intubated comatose patients. At LDS Hospital, we obtained additional history and performed a general physical examination and a neurologic examination of cranial nerves, pupils, muscles, deep-tendon reflexes, plantar reflexes, and cerebellar function before the first chamber session. Cerebellar dysfunction was considered to be present if finger-to-nose or heel-to-shin tests or rapid alternating movements were abnormal. Patients were either treated as outpatients or hospitalized for mechanical ventilation or because of coma, confusion, shock, cardiac ischemia, risk of suicide, or lack of social support. All patients consented to three protocol-directed sessions in monoplace hyperbaric chambers (Sechrist Industries) at intervals of 6 to 12 hours. In all patients, the first session was initiated within 24 hours after the end of the exposure to carbon monoxide (Fig. 1). After the first session, supplemental oxygen was used only if necessary to maintain the arterial oxygen saturation at a level higher than 90 percent.

To preserve blinding of patients and investigators regarding treatment-group assignment during the first chamber session, we provided all non-intubated patients with oxygen at a rate of 15 liters per minute with the use of a reservoir and a face mask that prevented rebreathing, chosen because it was commonly used by emergency departments in our area. During both hyperbaric-oxygen and normobaric-oxygen sessions, all intubated patients were mechanically ventilated with 100 percent oxygen. The patients in the hyperbaric-oxygen group were exposed to 100 percent oxygen at 3 and then 2 atmospheres absolute (304 kPa and 203 kPa, respectively) during the first chamber session and then to 100 percent oxygen at 2 atmospheres absolute for chamber sessions 2 and 3. Patients in the normobaric-oxygen group were exposed to air at 1 atmosphere absolute (101.3 kPa, or sea-level pressure) for all three chamber sessions. The chamber was pressurized to sea-level pressure in order to maintain blinding of patients and investigators.

For the first chamber session, the hyperbaric-oxygen protocol we used was recommended by others,[21] except for the addition of a five-minute air-protection period between 3 and 2 atmospheres absolute, which we added because of concern about hyperoxic seizures.[22] A previous clinical trial[8] was criticized for using hyperbaric oxygen at 2 atmospheres absolute,[23] rather than 2.5 to 3.0 atmospheres absolute,[21] so we used a hyperbaric-oxygen protocol at the higher recommended pressure (3 atmospheres absolute).[21] In the hyperbaric-oxygen protocol, three chamber sessions were used to prevent cognitive sequelae.[7] For hyperbaric-oxygen sessions 2 and 3, we reduced the pressure to 2 atmospheres absolute to reduce the likelihood of oxygen toxicity.[22] In the normobaric-oxygen protocol, chamber sessions 2 and 3 were provided in order to maintain blinding of patients and investigators (Fig. 2).

Respiratory therapists operated the controls for the chamber while observing pressure gauges visible only to them. These therapists maintained separate confidential records of the chamber sessions in order to ensure that others were unaware of the treatment-group assignments.

Collection of Data

At the time of enrollment, data concerning demographics, physiology, coexisting conditions, and medications, as well as details of the episode of carbon monoxide poisoning, were recorded. A physical examination was performed, and its results were recorded. A battery of neuropsychological tests, including tests of general orientation, digit span,[18] Trail Making (Parts A and B),[19] digit–symbol,[18] block design,[18] and story recall,[20] was administered immediately after the first and third chamber sessions and at 2 weeks, 6 weeks, 6 months, and 12 months.

The general orientation test is a 10-item list that measures the patient's orientation to person, place, and time, with scores ranging from 0 to 10 with lower scores representing better performance. Digit span, digit–symbol, and block design are subtests of the Wechsler Adult Intelligence Scale–Revised.[18] For the digit-span subtest, the subjects are read a numerical sequence and are asked to repeat the numbers in order, then, in an independent test, to repeat different digits in reverse order. Scores range from 0 to 14 for both parts of the test, with higher scores indicating better performance. The digit–symbol subtest requires subjects to reproduce symbols paired with digits, in blank boxes below randomly presented digits, as quickly as possible in 90 seconds; scores range from 0 to 90, with higher scores indicating better performance. In the block-design subtest, there are nine blocks colored red on two sides, white on two sides, and red and white on two sides. The subject is shown a card with a model design and, using the colored blocks, must copy the design accurately, as quickly as possible. Scores range from 0 to 51, with higher scores indicating better performance. The Trail Making Test Part A requires subjects to draw a line as quickly as possible connecting a series of numbers in sequence. The Trail Making Test Part B requires subjects to draw a line as quickly as possible connecting a series of numbers and letters in order, alternating num-

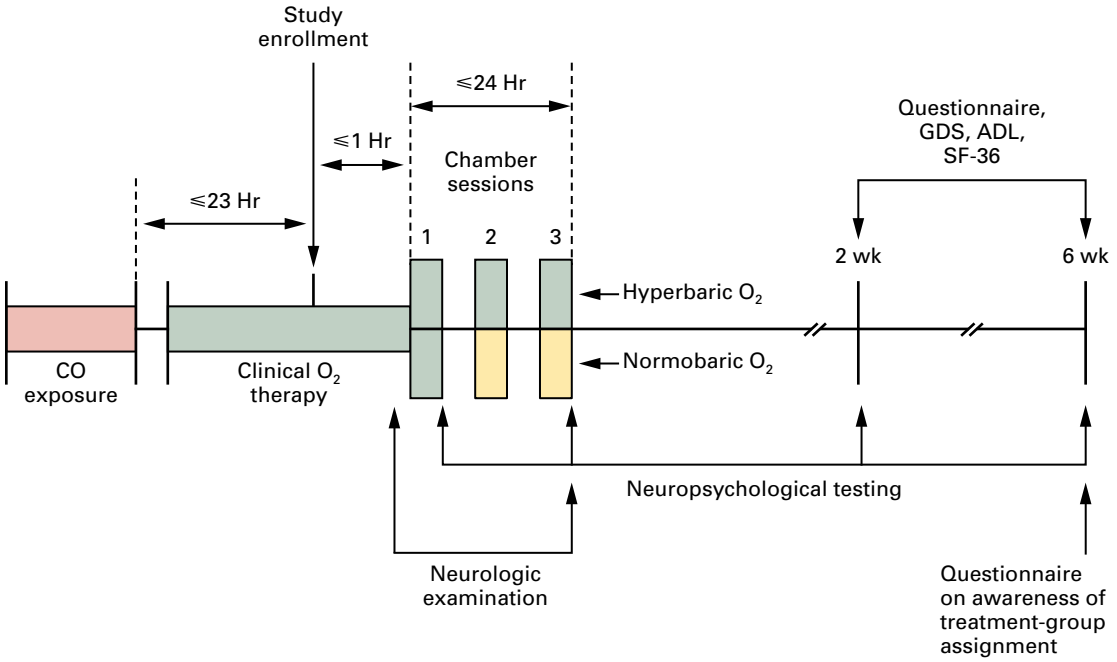


Figure 1. Study Design and Time Line.

Three chamber sessions were conducted, at intervals of 6 to 12 hours, within a 24-hour period. Neuropsychological testing included tests of general orientation, digit-span,[18] Trail Making Parts A and B,[19] digit–symbol,[18] block design,[18] and story recall.[20] These tests were administered after the first and third chamber sessions and at two and six weeks. Green areas indicate the delivery of oxygen, and yellow areas the delivery of air. GDS denotes Geriatric Depression Scale, ADL the Katz index of activities of daily living, and SF-36 Medical Outcomes Study 36-Item Short-Form General Health Survey.

ber and letter (e.g., 1-A-2-B). The scores range from 0 to 300 (for Parts A and B), with lower scores indicating better performance. The story-recall subtest of the Denman Neuropsychology Memory Scale[20] requires that subjects recall the details of a short story immediately after it is read to them. Scores are based on the number of items recalled from the story and range from 0 to 42, with higher scores indicating better performance.

We chose this battery of tests because its sensitivity in patients with acute carbon monoxide poisoning has been demonstrated.[24] A psychologist specializing in cognitive neuroscience or one of nine Ph.D. candidates in psychology, all of whom were unaware of the treatment-group assignments, tested the patients. All psychologists were deemed competent and reliable in test administration, as indicated by documented reproducibility of test results similar to that found among licensed, experienced neuropsychological testers. All tests are standardized, with known reliability and validity,[18-20,25] and were administered according to standardized formats[25] in quiet, private examination rooms.

After the third chamber session, trained investigators repeated the neurologic examination that had been performed after the first chamber session and also performed tests of olfaction, visual acuity, pin-prick and vibratory sensation, rapid pronation–supination of the forearms, normal gait, and heel–toe gait, as well as Romberg's test and the sharpened Romberg's test.[26] Evaluations at 2 weeks, 6 weeks, 6 months, and 12 months included the battery of neuropsychological tests, a questionnaire regarding symptoms of carbon monoxide poisoning that we developed for this study, the Geriatric Depression Scale,[27] the Katz index of activities of daily living,[28] and the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36).[29] Scores on the Geriatric Depression Scale range from 0 to 30, with higher scores indicating more severe depression. Scores on the SF-36 range from 0 to 100, with higher scores indicating better quality of life. At six weeks, patients also completed a questionnaire designed to determine whether or not they were aware of their treatment-group assignments.[30]

A priori, cognitive sequelae were considered to be present if, at six weeks, any T score for a neuropsychological subtest was more than 2 SD below the mean of demographically corrected standardized T scores (normal population mean [±SD], 50±10) or if two or more T scores for subtests were more than 1 SD below the mean.[31,32] If the patient reported difficulties with memory, attention, or concentration, then the T score on any neuropsychological subtest only had to be more than 1 SD below the mean of demographically corrected standardized T scores for cognitive sequelae to be considered to be present.

Statistical Analysis

The primary outcome was the incidence of cognitive sequelae six weeks after randomization. Secondary outcomes were analyzed in a hierarchical fashion: neuropsychological test scores obtained after the third chamber session, including the testing performed six weeks after the carbon monoxide poisoning; self-reports of symptoms of carbon monoxide poisoning at six weeks; scores on the Geriatric Depression Scale, the Katz index of activities of daily living, and the SF-36 at two and six weeks; and the results on the neurologic examination after the third chamber session.

We analyzed the primary outcome according to the intention-to-treat principle.[33] This analysis provides an assessment of the effectiveness of treatment as indicated by compliance with therapy and biologic effects.[33] For the purposes of the analysis of the primary

outcome, patients with missing data for neuropsychological tests at six weeks were assumed to have cognitive sequelae. For secondary outcomes, only patients with complete data were included in the analysis, because the aim of these analyses was to measure the efficacy of treatment.[33]

We calculated that the inclusion of 100 patients in each treatment group would provide the study with a statistical power of 80 percent to detect the difference between the published rates of cognitive sequelae of 5.8 percent[34] and 18.5 percent[35] (with a two-sided probability of a type I error of 0.05). The Statistical Data Center at LDS Hospital planned and performed interim analyses after the six-week data were available from 50, 100, and 150 enrolled patients, using a stopping rule requiring a two-sided P value of 0.0001, 0.001, and 0.01, respectively, for the three analyses. The statisticians and investigators, who were blinded to patients' treatment-group assignments, had access to the results of the interim analyses. The final analysis of the primary outcome for the anticipated 200 patients would have shown a significant difference if the P value were less than 0.0389. This alpha spending-function technique maintained an overall P value of less than 0.05. Early termination of the study was planned if one of the interim analyses showed hyperbaric-oxygen treatment to be effective, ineffective, or deleterious.[36] For secondary outcome variables, a P value of less than 0.05 was considered to indicate statistical significance. A Bonferroni's correction was used for the six neuropsychological subtests, with a level of significance of less than 0.008 ($0.05 \div 6$).

Our a priori end point was the incidence of cognitive sequelae at six weeks. We also report rates of cognitive sequelae at 6 and 12 months, although these end points were not included in the study design. We assumed a priori that cognitive sequelae developing after six weeks would not be caused by carbon monoxide poisoning.[2-5,6,7,11]

All statistical methods were determined a priori. All data were analyzed by investigators and statisticians who were blinded to the treatment-group assignments. We used Student's t-test, logistic regression, Pearson chi-square, or Fisher's exact tests to compare the treatment groups in terms of base-line variables; the incidence of cognitive sequelae at 6 weeks, 6 months, and 12 months; the frequency of symptoms of carbon monoxide poisoning; and the frequency of abnormal neurologic findings. We used multivariable logistic regression to analyze the primary outcome, testing for treatment effects while adjusting for stratification and for additional factors associated with both treatment-group assignment and cognitive sequelae. For the primary outcome, the prespecified analysis was unadjusted. We used repeated-measures analysis of variance, with time as the variable within groups and treatment as the variable between groups, to test for treatment-related differences in the scores on the battery of neuropsychological tests, the Geriatric Depression Scale, the Katz index of activities of daily living, and the SF-36. Unadjusted odds-ratio estimates and 95 percent confidence intervals were calculated by logistic regression. Results are reported as percentages, or means ±SD. For the Geriatric Depression Scale, results of repeated-measures analysis of variance are reported as marginal means ±SE. All P values are two-sided.

RESULTS

Primary Outcome

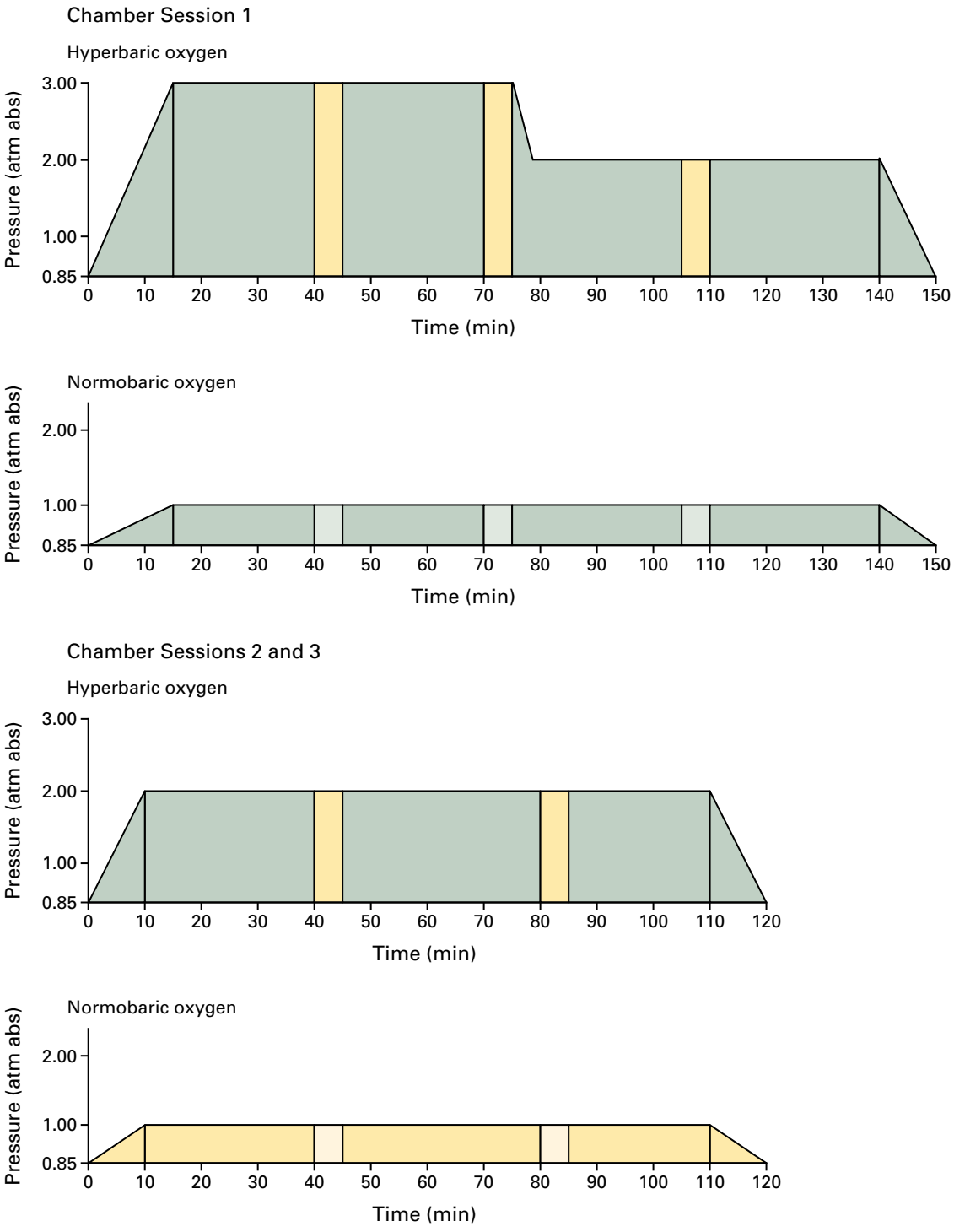
A total of 76 patients were randomly assigned to each treatment group. Seventy-five patients in the hyperbaric-oxygen group and 72 in the normobaric-oxygen group completed neuropsychological testing at six weeks (Fig. 3). Base-line characteristics were similar in the two groups (Table 1), although cerebellar dysfunction before treatment was more frequent in the normobaric-oxygen group (15 percent, as compared with 4 percent in the hyperbaric-oxygen group; $P=0.03$). The presence of cerebellar dysfunction before treatment, regardless of treatment-group assignment, was associated with a higher incidence of cognitive sequelae than was the absence of such dysfunction (odds ratio, 5.71 [95 percent confidence interval, 1.69 to 19.31]; $P=0.005$). The trial was stopped after the third interim analysis, which included 150 patients, because hyperbaric oxygen was judged to be efficacious ($P<0.01$).

By the time the results of the interim analysis became available, 152 patients had been enrolled. For all 152 patients in the intention-to-treat population, cognitive sequelae at six weeks were less frequent in the hyperbaric-oxygen group (25.0 percent) than in the normobaric-oxygen group (46.1 percent; unadjusted odds ratio, 0.39 [95 percent confidence interval, 0.20 to 0.78]; $P=0.007$) (Table 2). The same was true for the 147 patients with complete data on neuropsychological tests at six weeks: cognitive sequelae were less frequent at six weeks among patients who received hyperbaric-oxygen treatment (24.0 percent) than among those who received normobaric oxygen (43.1 percent, $P=0.01$) (Table 2).

After adjustment by logistic regression for cerebellar dysfunction before treatment and for stratification variables, hyperbaric oxygen still appeared to be the more effective therapy (odds ratio, 0.45 [95 percent

Figure 2 (facing page). Design of Chamber Sessions, Showing the Pressure and Duration of Oxygen Exposure for Patients in the Hyperbaric-Oxygen Group and Patients in the Normobaric-Oxygen Group.

Dark green areas indicate the delivery of oxygen, and yellow areas the delivery of air; vertical strips of a different shade from the background represent five-minute "protection periods," during which patients used SCUBA-type demand regulators, mouthpieces, and noseclips (or mechanical ventilators, if intubated), as air was delivered to patients in the hyperbaric-oxygen group (in order to reduce the risk of oxygen toxicity[22]) and 100 percent oxygen was delivered to those in the normobaric-oxygen group during chamber session 1. The pressure of 0.85 atmosphere absolute (atm abs) (85.5 kPa, or 642 mm Hg) is the normal atmospheric pressure at LDS Hospital (altitude, 1500 m). Alveolar partial pressures of oxygen for the patients in the hyperbaric-oxygen group were approximately 2200 mm Hg at 3 atmospheres absolute and 1470 mm Hg at 2 atmospheres absolute. Alveolar partial pressures of oxygen for the patients in the normobaric-oxygen group were approximately 530 mm Hg while they were breathing oxygen (estimated fractional inspired oxygen concentration, 0.80) and 108 mm Hg while they were breathing air at sea-level pressure. During normobaric-oxygen sessions 2 and 3, patients were exposed to 1 atmosphere absolute and breathed air (with supplemental oxygen if it was clinically necessary to maintain the arterial oxygen saturation at 90 percent or if they were intubated and mechanically ventilated).


Chamber Session 1
Hyperbaric oxygen
Pressure (atm abs)
3.00
2.00
1.00
0.85
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150
Time (min)
Normobaric oxygen
Pressure (atm abs)
2.00
1.00
0.85
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150
Time (min)
Chamber Sessions 2 and 3
Hyperbaric oxygen
Pressure (atm abs)
3.00
2.00
1.00
0.85
0 10 20 30 40 50 60 70 80 90 100 110 120
Time (min)
Normobaric oxygen
Pressure (atm abs)
2.00
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0 10 20 30 40 50 60 70 80 90 100 110 120
Time (min)

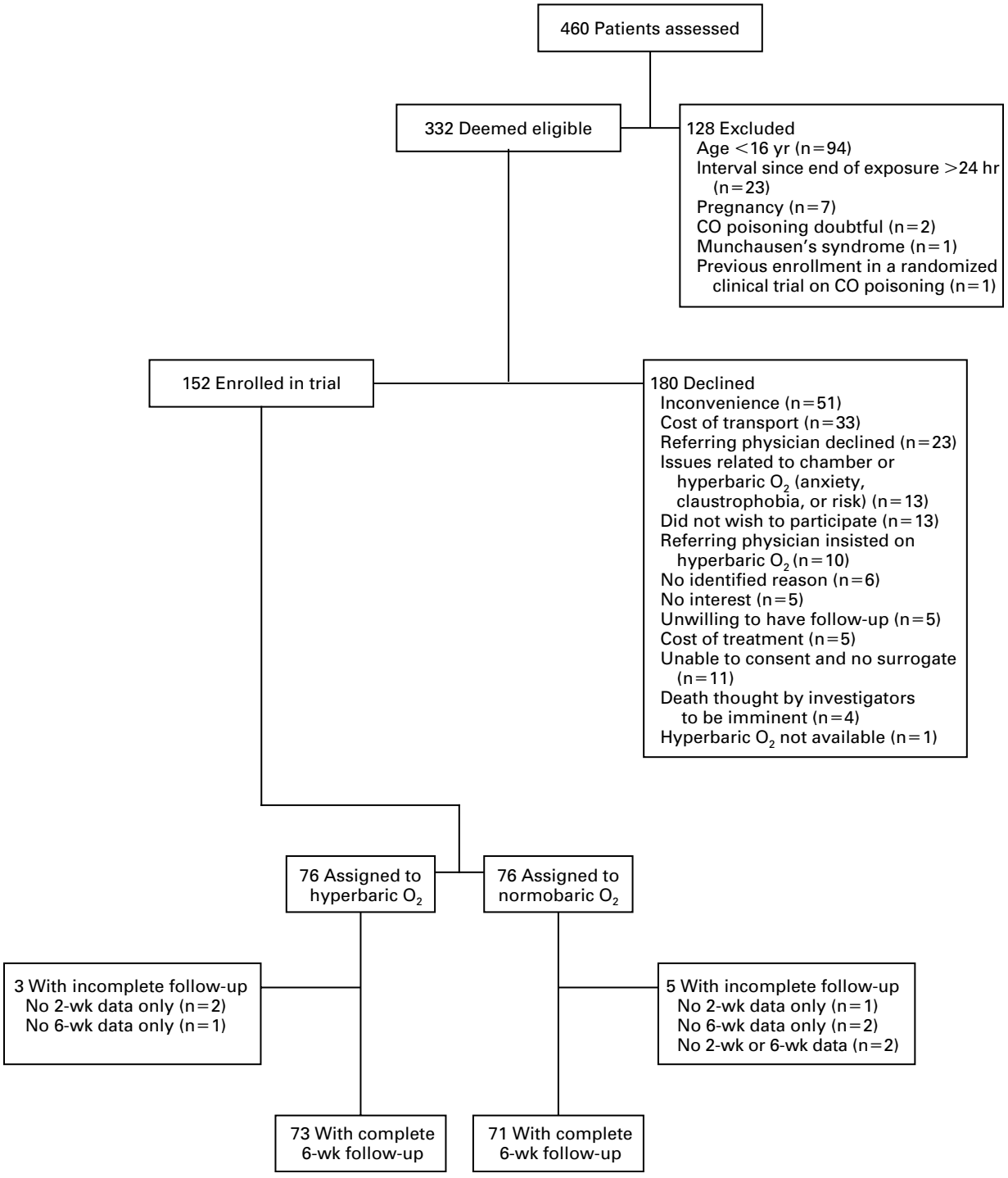

Figure 3. Numbers of Patients Assessed, Enrolled, and Completing Follow-up.
In normobaric-oxygen therapy, 100 percent oxygen was given at sea-level pressure.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	HYPERBARIC-OXYGEN GROUP (N=76)	NORMOBARIC-OXYGEN GROUP (N=76)
Age (yr)	35±10	36±15
Female sex (%)	29	29
English as primary language (%)	96	91
Educational level (yr)	12.3±3.0	11.9±3.8
Suicide attempt (%)	36	26
Initial symptoms (%)		
Headache	84	85
Weakness or lethargy	63	59
Dizziness	57	59
Nausea or vomiting	63	63
Difficulties with memory or confusion	44	37
Cerebellar dysfunction (%)†	4	15
Intubation (%)‡	8	8
Hospital admission (%)	14	12
Source of carbon monoxide (%)		
Internal combustion engine	62	47
Furnace or heater	36	41
Stratification variables (%)		
Loss of consciousness	49	50
Interval between end of exposure to carbon monoxide and first chamber session ≥6 hr	40	36
Age ≥40 yr	32	36
Interval between end of exposure to carbon monoxide and first chamber session (hr)§	5.8±2.9	5.7±2.9
In group with interval <6 hr	4.3±0.8	4.5±0.9
In group with interval ≥6 hr	8.6±3.4	9.0±3.8
Duration of exposure to carbon monoxide (hr)	13±41	22±64
Interval between end of exposure to carbon monoxide and initial carboxyhemoglobin measurement (hr)	1.5±1.2	1.8±2.5
Initial carboxyhemoglobin measurement (%)	25±9.6	25±8.7
Interval between initial carboxyhemoglobin measurement and first chamber session (hr)	4.3±2.7	3.9±1.9
Half-life of carboxyhemoglobin (min)¶	85±30	84±21
Carboxyhemoglobin level estimated at initial entry into chamber (%)		
In 83 patients with data on half-life‖	4.5±2.3	5.7±2.0
In all 152 patients**	4.3±2.9	4.6±3.1
Interval between end of exposure to carbon monoxide and initiation of clinical oxygen treatment (hr)	1.0±1.2	1.2±2.5
Duration of clinical oxygen treatment before chamber sessions (hr)	4.5±2.6	4.5±2.2

*Plus–minus values are means ±SD. Because of rounding, not all percentages total 100. All differences are nonsignificant unless otherwise indicated.

†P=0.03 for the comparison between groups.

‡Intubated and mechanically ventilated patients in the normobaric-oxygen group were treated with 100 percent oxygen while they were in the chamber. When they were not in the chamber, they received a fractional inspired oxygen concentration sufficient to maintain an arterial saturation of oxygen of more than 90 percent.

§Patients were stratified on the basis of this interval (<6 hours or ≥6 hours); in the hyperbaric-oxygen group, there were 50 patients in the shorter-interval subgroup and 25 in the longer-interval subgroup, and 1 declined treatment in the chamber; in the normobaric-oxygen group, there were 56 patients in the shorter-interval subgroup and 20 in the longer-interval subgroup.

¶The half-life of carboxyhemoglobin was calculated on the basis of two carboxyhemoglobin measurements obtained at different times (t_1 and t_2) in patients with a final carboxyhemoglobin value of at least 4 percent.[37] These measurements were obtained in 36 patients in the hyperbaric-oxygen group and 47 patients in the normobaric-oxygen group, before they began treatment in the chamber and while they were breathing 100 percent normobaric oxygen. The half-life of carboxyhemoglobin is calculated as $(t_2-t_1)\times\ln(2)\div\ln(\text{carboxyhemoglobin at } t_1\div\text{carboxyhemoglobin at } t_2)$.[37]

‖P=0.02 for the comparison between groups.

**In 69 patients, missing values were imputed on the basis of the data on the half-life of carboxyhemoglobin in the other 83 patients (mean half-life, 84.6 minutes).

TABLE 2. OUTCOMES AT 6 WEEKS, 6 MONTHS, AND 12 MONTHS AFTER ENROLLMENT.*

OUTCOME	HYPERBARIC-OXYGEN GROUP (N=76)	NORMOBARIC-OXYGEN GROUP (N=76)	UNADJUSTED ODDS RATIO (95% CI)†	P VALUE
	no./total no. (%)			
Cognitive sequelae				
At 6 wk				
Intention-to-treat population	19/76 (25.0)	35/76 (46.1)	0.39 (0.20–0.78)	0.007
Patients with complete data	18/75 (24.0)	31/72 (43.1)	0.42 (0.21–0.85)	0.01
Results on cerebellar testing before treatment				
Normal	16/69 (23.2)	23/59 (39.0)	0.47 (0.22–1.02)	0.05
Abnormal	1/3 (33.3)	9/11 (81.8)	0.11 (0.01–1.92)	0.18
At 6 mo				
Intention-to-treat population	16/76 (21.1)	29/76 (38.2)	0.43 (0.21–0.89)	0.02
Patients with complete data	10/58 (17.2)	21/59 (35.6)	0.38 (0.16–0.90)	0.03
At 12 mo				
Intention-to-treat population	14/76 (18.4)	25/76 (32.9)	0.46 (0.22–0.98)	0.04
Patients with complete data	9/62 (14.5)	18/66 (27.3)	0.45 (0.19–1.10)	0.08
Symptoms				
Reported by patient at 6 wk				
Difficulties with memory	21/75 (28.0)	37/72 (51.4)	0.37 (0.19–0.73)	0.004
Difficulties with attention or concentration	24/75 (32.0)	31/72 (43.1)	0.62 (0.32–1.22)	0.17

*The five patients who did not have data on neuropsychological tests at six weeks were assumed to have cognitive sequelae at that time point. Cognitive sequelae present at 6 or 12 months were assumed not to be due to carbon monoxide poisoning if they had not been present at 6 weeks.[2,4-7,11] Patients with cognitive sequelae at 6 weeks who had missing data at 6 or 12 months were assumed to have cognitive sequelae at those time points.

†The normobaric-oxygen group was the reference group. CI denotes confidence interval.

confidence interval, 0.22 to 0.92]; P=0.03). Patients treated with hyperbaric oxygen were less likely to have cognitive sequelae at six weeks than were those treated with normobaric oxygen, whether they had had normal (P=0.05) or abnormal (P=0.18) cerebellar function before treatment (Table 2). Failure to complete the chamber sessions was more common in the hyperbaric-oxygen group (14 of 76 [18.4 percent]) than in the normobaric-oxygen group (3 of 76 [3.9 percent], P=0.005). The first hyperbaric-oxygen treatment was stopped prematurely because of anxiety (in seven patients), tympanic-membrane rupture (in one patient), and cough (in one patient). The second or third hyperbaric-oxygen treatment was omitted due to difficulty with equalization of middle-ear pressure (in four patients) or failure to return for treatment (in one patient). The second or third normobaric-oxygen session was omitted because of failure to return (in three patients). The frequency of cognitive sequelae among patients who completed three hyperbaric-oxygen sessions (15 of 62 patients [24.2 percent]) was not significantly different from that among patients who did not complete the three sessions (4 of 14 patients [28.6 percent], P=0.74). Blinding of the patients[30] and the investigators was maintained throughout the study and the data analysis performed at 12 months.

Secondary Outcomes

T scores for neuropsychological tests did not differ significantly between the treatment groups (P=0.31). The T scores showed improvement from testing immediately after the third chamber session to six weeks (P<0.001), with similar rates of improvement in both treatment groups (P=0.62). Only the treatment-group differences in T scores for the digit-span subtest (P=0.06) and the Trail Making Test Parts A (P=0.03) and B (P=0.06) approached statistical significance favoring hyperbaric-oxygen therapy (Table 3).

Patients treated with hyperbaric oxygen reported fewer difficulties with memory (P=0.004) and with attention or concentration (P=0.17) (Table 2). The mean (±SD) score on the Geriatric Depression Scale improved from two weeks (9.4±8.1) to six weeks (8.3±7.8, P=0.02). Although the difference was not statistically significant, patients treated with hyperbaric oxygen reported less depression overall (marginal mean score [±SE], 8.0±0.9) than those treated with normobaric oxygen (9.7±0.9, P=0.17). Scores on the Katz index of activities of daily living were normal for most patients regardless of treatment-group assignment or time of assessment. Four patients reported (at two or six weeks) a minor problem with activities of daily living that they deemed unrelated to carbon

monoxide poisoning. We found no treatment-related differences in scores on the subscales of the SF-36. Between two weeks and six weeks, mean scores improved for social function (from 73.0±24.9 to 81.3±24.1, P<0.001), physical role (from 61.0±47.2 to 73.1±40.0, P=0.003), mental health (from 64.3±23.7 to 69.5±22.8, P=0.001), and energy (from 51.2±22.6 to 58.8±22.6, P<0.001).

Nystagmus after the third chamber session was more frequent in patients treated with hyperbaric oxygen (12.0 percent) than in those treated with normobaric oxygen (2.7 percent; odds ratio, 4.84 [95 percent confidence interval, 1.01 to 23.22]; P=0.05). There were no significant differences between the treatment groups in terms of other elements of the detailed neurologic examination.

Outcomes at 6 and 12 Months

Cognitive sequelae at 6 months and 12 months were less frequent in the hyperbaric-oxygen group than in the normobaric-oxygen group, both according to the intention-to-treat analysis (P=0.02 at 6 months, P=0.04 at 12 months) and according to the efficacy analysis (P=0.03 at 6 months, P=0.08 at 12 months) (Table 2).

DISCUSSION

Hyperbaric-oxygen therapy reduced the frequency of cognitive sequelae by 46 percent, as assessed six weeks after acute, symptomatic carbon monoxide poisoning. Thereafter, there was improvement in both groups of patients, but at 12 months, there remained a difference in the frequency of cognitive sequelae. At six weeks, patients with cognitive sequelae had moderate-to-severe cognitive impairments: 20 percent of the patients fell below the 5th percentile and 33 percent fell below the 16th percentile of the normal distribution of cognitive function.[25] They communicated and performed activities of daily living normally but found activities that require executive function, memory, or attention or concentration skills to be challenging or impossible. These problems are similar to cognitive sequelae that have been observed in patients who were assessed several years after elective coronary-artery bypass surgery.[38] Our findings suggest that prevention of cognitive sequelae in one patient assessed six weeks after acute carbon monoxide poisoning requires hyperbaric-oxygen treatment of only five patients.

Although hyperbaric-oxygen therapy can cause hyperoxic seizures, aural barotrauma, anxiety, and oxidative stress,[3,10,14,22] the ability to administer three hyperbaric-oxygen treatments in our study was limited primarily by anxiety and aural barotrauma. We chose to provide three hyperbaric-oxygen sessions because a retrospective report suggested that the use of more than two treatments resulted in better outcomes than the use of a single treatment.[7] We provided the three sessions within a 24-hour period because we anticipated that patients' compliance would be better during a shorter period than it would during a longer one. Since our trial began, a survey was published indicat-

TABLE 3. T SCORES FOR NEUROPSYCHOLOGICAL SUBTESTS.*

SUBTEST†	HYPERBARIC-OXYGEN GROUP (N=71)	NORMOBARIC-OXYGEN GROUP (N=69)	P VALUE
	T score		
Digit span			
After chamber session 1	42.6±13.7	39.7±12.9	0.19
After chamber session 3	44.9±12.6	43.0±10.3	0.06
2 Wk after enrollment	47.5±13.0	43.9±12.0	
6 Wk after enrollment	49.3±11.7	44.3±10.8	
Trail Making			
Part A			
After chamber session 1	43.9±15.2	41.2±15.0	0.30
After chamber session 3	51.0±13.1	47.6±13.5	0.03
2 Wk after enrollment	54.9±13.5	49.2±13.2	
6 Wk after enrollment	55.6±11.5	51.5±15.8	
Part B			
After chamber session 1	44.5±15.1	41.0±15.7	0.18
After chamber session 3	51.7±13.7	48.4±14.6	0.06
2 Wk after enrollment	53.9±13.6	50.3±15.1	
6 Wk after enrollment	56.8±13.5	51.4±14.9	
Digit–symbol			
After chamber session 1	46.7±14.7	46.2±14.1	0.83
After chamber session 3	54.5±13.4	52.8±12.5	0.26
2 Wk after enrollment	58.3±13.9	56.2±11.7	
6 Wk after enrollment	59.5±12.2	56.4±12.3	
Block design			
After chamber session 1	52.9±15.0	50.4±15.8	0.35
After chamber session 3	57.7±12.6	57.3±12.6	0.44
2 Wk after enrollment	60.9±12.5	59.4±12.7	
6 Wk after enrollment	63.4±11.6	60.8±13.6	
Story recall			
After chamber session 1	37.5±14.5	39.4±14.7	0.45
After chamber session 3	50.8±13.2	49.7±12.6	0.47
2 Wk after enrollment	53.0±13.3	51.2±11.7	
6 Wk after enrollment	53.0±11.8	51.8±12.4	

*Plus–minus values are means ±SD. The mean demographically corrected standardized T score in a normal population was 50±10 for each subtest.[31,32] Numbers of patients given are the numbers of patients with complete data for neuropsychological tests from all four evaluations. Four patients in the hyperbaric-oxygen group and three in the normobaric-oxygen group who had data for neuropsychological tests at six weeks lacked complete data for neuropsychological tests after chamber session 3 or for those at two weeks. P values for comparisons of the T scores in the two groups after chamber session 1 are derived from t-tests. The second P value given for each test is for the comparison of the groups in terms of the three T scores obtained after chamber session 3, at two weeks, and at six weeks; these P values were derived by repeated-measures analysis of variance.

†Digit span, digit–symbol, and block design are subtests of the Wechsler Adult Intelligence Scale–Revised.[18] For the digit-span subtest, scores range from 0 to 14 for both parts of the test, with higher scores indicating better performance. For the digit–symbol subtest, scores range from 0 to 90, with higher scores indicating better performance. For the block-design subtest, scores range from 0 to 51, with higher scores indicating better performance. The scores for the Trail Making Test Parts A and B range from 0 to 300, with lower scores indicating better performance. For the story-recall subtest of the Denman Neuropsychology Memory Scale,[20] scores range from 0 to 42, with higher scores indicating better performance.

ing that 74 percent of practitioners who provide hyperbaric-oxygen treatment use only a single hyperbaric-oxygen treatment for acute carbon monoxide poisoning,[17] even though there has been no systematic clinical evaluation of the optimal dose or frequency of such treatment. Our trial did not assess the merits of a single hyperbaric-oxygen session as compared with three hyperbaric-oxygen sessions.

Because of methodologic differences, it is difficult to compare the results of the several randomized clinical trials in patients with acute carbon monoxide poisoning.[5,8,9,15] For example, Scheinkestel et al.[9] reported that hyperbaric oxygen might worsen the outcome in patients with carbon monoxide poisoning, but our trial differed substantially from theirs in terms of the proportion of patients who were intubated (7.9 percent, vs. 19.0 percent in the study by Scheinkestel et al.), the duration of exposure to carbon monoxide (18.0 hours vs. 2.5 hours), the interval between the end of the exposure to carbon monoxide and the initiation of hyperbaric-oxygen therapy (5.8 hours vs. 7.1 hours), the randomization method (equal proportions vs. clustering), the follow-up rate (97 percent vs. 46 percent), the proportion of patients who had carbon monoxide poisoning as a result of a suicide attempt (31 percent vs. 69 percent), the type of statistical analysis (intention-to-treat analysis vs. efficacy analysis), and the oxygen-treatment protocols (three hyperbaric-oxygen treatments in a 24-hour period vs. three to six treatments over a period of three to six days). In the group treated with normobaric oxygen, we provided oxygen therapy for a mean duration of 6.9±2.2 hours, whereas Scheinkestel et al. provided high-flow supplemental oxygen for a mean of three days.

Our patients had nearly normal carboxyhemoglobin concentrations just before the first chamber session, a finding that suggests the presence of therapeutic mechanisms that are independent of elevated carboxyhemoglobin levels at the time of hyperbaric-oxygen therapy.[3,10,11,13,39-41] Although they have not been evaluated in humans, mechanisms by which hyperbaric oxygen might reduce cognitive sequelae after carbon monoxide poisoning include the preservation of adenosine triphosphate activity, modulation of ischemia–reperfusion injury, and prevention of lipid peroxidation.[39,42]

We selected an end point that was evaluated at six weeks so that we could identify all delayed cognitive sequelae.[2-7,11] We included the data on the 6-month and 12-month evaluations because of the importance of long-term outcomes. However, decreasing follow-up rates and other psychosocial and medical factors unrelated to carbon monoxide poisoning may have influenced the neuropsychological test results obtained 6 and 12 months after carbon monoxide poisoning.

In summary, treatment of patients with acute, symptomatic carbon monoxide poisoning with three hyperbaric-oxygen sessions within a 24-hour period appears to reduce the rate of cognitive sequelae 6 weeks and 12 months later. Our results support the use of hyperbaric oxygen in patients with acute carbon monoxide poisoning.

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