Intensive Care Med (2011) 37:486–492
DOI 10.1007/s00134-010-2093-0

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Hyperbaric oxygen therapy for acute domestic carbon monoxide poisoning: two randomized controlled trials

Received: 3 May 2010
Accepted: 25 September 2010
Published online: 2 December 2010

The full trial protocol can be obtained by direct contact with the corresponding author.

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Abstract *Introduction:* Although hyperbaric oxygen therapy (HBO) is broadly used for carbon monoxide (CO) poisoning, its efficacy and practical modalities remain controversial. *Objectives:* To assess HBO in patients poisoned with CO. *Design:* Two prospective randomized trial on two parallel groups. *Setting:* Critical Care Unit, Raymond Poincaré Hospital, Garches, France. *Subjects:* Three hundred eighty-five patients with acute domestic CO poisoning. *Intervention:* Patients with transient loss of consciousness (trial A, $n = 179$) were randomized to either 6 h of normobaric oxygen therapy (NBO; arm A0, $n = 86$) or 4 h of NBO plus one HBO session (arm A1, $n = 93$). Patients with initial coma (trial B, $n = 206$) were randomized to either 4 h of NBO plus one HBO session (arm B1, $n = 101$) or 4 h of NBO plus two 2 HBO sessions (arm B2, $n = 105$). *Primary endpoint:* Proportion of patients with complete recovery at 1 month. *Results:* In trial A, there was no evidence for a difference in 1-month complete recovery rates with and without HBO [58% compared to 61%; unadjusted odds ratio, 0.90 (95% CI, 0.47–1.71)]. In trial B, complete recovery rates were significantly lower with two than with one HBO session [47% compared to 68%; unadjusted odds ratio, 0.42 (CI, 0.23–0.79)]. *Conclusion:* In patients with transient loss of consciousness, there was no evidence of superiority of HBO over NBO. In comatose patients, two HBO sessions were associated with worse outcomes than one HBO session.

Keywords Carbon monoxide poisoning · Oxygen · Hyperbaric oxygen therapy · Coma · Clinical trials

Introduction

Carbon monoxide (CO) is a colorless, odorless, and highly toxic gas usually produced during incomplete carbon combustion. CO poisoning is common, and sources of CO include fires, improperly functioning heaters, motor vehicle emissions, and industrial accidents. CO diffuses readily within the alveoli and has far greater affinity than oxygen for essential biological compounds such as hemoglobin and cellular oxidative enzymes. Thus, CO poisoning causes cellular hypoxia. However, the mechanisms of its complications remain unclear [1].

CO poisoning can cause immediate death, non-specific hypoxia-related neurological and cardiac manifestations, rhabdomyolysis, and abnormal liver function. Neurological abnormalities include persistent neurological sequelae (PNS) that may improve over time and delayed neurological sequelae (DNS) that occur after a symptom-free interval and vary widely in severity [1].

CO poisoning management includes removing patient from the source of CO and supportive care. Normobaric oxygen therapy (NBO) induces a fivefold decrease in carboxyhemoglobin half-life and is the standard treatment. Although hyperbaric oxygen therapy (HBO) produces a larger reduction in carboxyhemoglobin half-life, its benefit:risk ratio is still debated.

Clinical trials comparing NBO and HBO [2–7] have yielded conflicting results, as a result probably of differences in population, CO poisoning severity, interventions, and evaluation criteria. Only two studies focused on pure CO poisoning [4, 5]. Severity of intoxication varied between studies from symptom-free to comatose patients. The practical modalities of HBO dives differed in maximum pressure from 2 to 3 ATA, in number of sessions from one to three sessions, and in the addition or not of NBO. Only two studies used 'sham dives' [6, 7]. Duration of follow-up varied from 1 month [4–6] to 1 year [7], and one study assessed only surrogate outcomes [3]. In a recent systematic review, the odds ratio for neurological deficit was 0.78, 95% CI 0.54–1.12, with heterogeneity across the studies (squared $I = 46.3\%$) [8].

Hence, we compared NBO to HBO in patients with transient loss of consciousness, and, in comatose patients, NBO with one or two HBO sessions.

Methods

The study was approved by the ethics committee of the Société de Réanimation de Langue Française. Patients were recruited between October 1989 and January 2000 at Raymond Poincaré Teaching Hospital, Garches, France. Written informed consent was obtained from patients or their relatives.

Trial design and registration

We performed two randomized controlled trials on two parallel groups. Trial A included non-comatose patients, and trial B included comatose patients. These trials were retrospectively registered at https://register.clinicaltrials.gov with number NCT01100515 for trial A and NCT01099995 for trial B.

Patients

We included patients aged 15 years or more, and admitted for domestic CO poisoning within 12 h after the end of CO exposure. Diagnosis was based on a carboxyhemoglobin level at presentation >10 or >5%, in smokers and non-smokers, respectively. CO was measured using a spectrophotometer (CO oxymeter® 2000, Corning Medical). Non-inclusion criteria were (1) mixed poisoning (e.g., CO plus a drug or other toxic gases such as those found in fire smoke); (2) suicide attempt; (3) pregnancy; (4) contraindications to HBO (circulatory collapse or pneumothorax); (5) technical obstacles to HBO; (6) normal consciousness; (7) non-domestic CO poisoning; (8) difficulty in establishing initial loss of consciousness or coma; and (9) consent refusal.

The diagnosis was based on the circumstances of CO exposure and, if appropriate, on tests conducted by the public health service to measure CO production at home. We estimated exposure duration (from presumed onset to end of CO exposure) and time to randomization (from end of CO exposure to randomization).

Randomization

Eligible patients were classified by attending physicians into those who experienced transient loss of consciousness (malaise, syncope; trial A) or coma as confirmed by a household member or a rescuer (trial B). Patients were randomized (1:1) by using numbered sealed envelopes. An independent statistician prepared a computer-generated allocation sequence for each trial (A and B).

Interventions

Trial A patients were treated with 6 h of NBO (A0) or with 4 h of NBO plus one HBO session (A1). Trial B patients with 4 h of NBO plus one HBO session (B1)—the same treatment as in A1- or with 4 h of NBO and two HBO sessions within an interval of 6 (at minimum) to 12 h (at maximum). NBO and HBO were started as early as possible after randomization.

NBO and HBO were given through a facemask or by mechanical ventilation, as required, at a fraction of inspired oxygen (FiO_2) of 100%, at 1.0 or 2.0 ATA, respectively. Each HBO session lasted 2 h in a multiplace chamber (Comex Pro); each session included 30 min for compression, 1 h at a 2 ATA plateau pressure, and 30 min for decompression. Diazepam (10 mg) was injected intramuscularly before each HBO session to prevent oxygen-induced seizures. Carboxyhemoglobin was measured at treatment completion. Supportive treatment was provided as needed.

Follow-up

Vital signs, clinical symptoms, and laboratory data were monitored until hospital discharge. Patients were followed-up to 1 month after randomization. At 1 month, patients completed a self-assessment questionnaire with

yes/no items about headaches, tiredness, memory impairment, difficulty in concentrating, difficulty in sleeping, visual disorders, and new difficulties with social or professional activities. They underwent a thorough physical examination at the ICU outpatient clinic by one intensive care physician qualified in neurology who remained blinded to patients' treatment arm. In patients who could not come back to the hyperbaric center, the 1-month visit was performed by patient's general practitioner.

Definitions

Coma was defined as a Glasgow coma score of <8. Transient loss of consciousness or malaise or syncope was defined as normal consciousness at the time the patient was rescued and he/she could not recall what happened and/or reported that he/she had loss consciousness. Complete recovery was defined as an absence of symptoms reported on the self-assessment questionnaire with a normal physical exam (including normal neuropsychological functions). Moderate sequels were defined as one or more symptoms on the questionnaire and normal physical findings, and severe sequels as any objective abnormality at patient's examination. Neurological sequels were considered persistent when present both at hospital discharge and at 1-month evaluation. Delayed neurological sequelae were any neurological manifestations that appeared between hospital discharge and 1-month evaluation.

Study outcomes

The primary end point was complete recovery as defined above. Secondary end points were 1 month rates of PNS, DNS, and proportion of patients who resumed their former occupational activity. Tertiary endpoints included difference in carboxyhemoglobin levels before/after treatment completion and adverse events.

Sample sizes

Sample sizes for trial A and B were calculated separately. In trial A, assuming an 1 month recovery rate of 40% in the reference group (A0), 245 patients were needed per treatment arm to detect an absolute difference of at least 15% in recovery rates with a type I error of 0.05 and a type II error of 0.10 using a two-sided test. In trial B, the number of patients per treatment arm required to detect a 15% difference between the two treatments was 240 assuming 35% recovery rates in the reference group (B1), a type I error of 0.05, and a type II error of 0.10 using a two-sided test. Thus, the total number of patients required was 970 patients, 490 in trial A and 480 in trial B.

One interim analysis was scheduled after inclusion of 300 patients to allow premature study termination if data suggested a large difference between treatment arms, serious treatment-related adverse events, difficulties in conducting the trial, or futility [9].

Statistical analysis

Statistical analysis was performed on an intention-to-treat basis. The same statistical analysis procedure was carried out separately in trials A and B. First, non-parametric Wilcoxon rank sum tests and Fisher's exact tests were used to compare treatment arms at baseline. Then, complete recovery rates in the two treatment arms were compared by Fisher's exact test. Odds ratio (OR) with 95 percent confidence interval (95% CI) was computed from logistic models to estimate the strength of the association between the randomly allocated treatment and the complete recovery rate. Finally, secondary end points were compared using Fisher's exact tests (severe neurological impairment, return to work after 1 month, and treatment-related adverse events) and non-parametric Wilcoxon rank sum test (change in carboxyhemoglobin from baseline to treatment completion). Absolute and relative changes in carboxyhemoglobin levels were evaluated. Given some missing values on the outcome, we performed sensitivity analysis presenting a range of estimates under alternative assumptions about the missing-data mechanism. Graphical displays of the results of all possible allocations of cases with missing binary outcomes, as proposed by Hollis [10], were provided.

All statistical tests were two-sided, with type I error set at 0.05. Owing to the scheduled interim analysis, p values of 0.029 or less were used to define statistical significance. Statistical analysis was performed using SAS 9.2 (SAS Inc, Cary, NC) and R 2.10.1 (http://www.R-project.org) packages. The code for producing the graphical sensitivity was derived from that provided by Hollis on S-Plus software [10].

Results

The trial was terminated prematurely after the interim analysis (January 2000), based on a total of 385 patients, showing that, in comatose patients (trial B), the 1 month complete recovery rate was lower in the "two HBO sessions" arm compared to the "one HBO session" arm (47 vs. 68%, $p = 0.007$). Furthermore, in trial A patients, recovery rates were close (61% in control arm vs. 58% in experimental arm), suggesting futility of treatment

continuation. Accordingly, we decided to terminate trial A also.

From October 1989 to January 2000, 735 patients were admitted for CO poisoning, and 385 were randomized (Fig. 1). In each trial, treatment arms were well matched (Table 1). We examined treatment effects separately in each trial.

Trial A

Of the 179 patients included in trial A, 6 had coma before admission; these misclassified patients were kept in trial A for analysis. Eighty-six patients were then allocated to NBO alone (A0 arm) and 93 to NBO plus one HBO session (A1 arm). Of 179 patients, 174 had normal consciousness at randomization, and 5 had confusion. At 1 month, 26 patients (14.5%) were lost to follow-up. Complete recovery rates were roughly the same in both arms [61% compared with 58%; $p = 0.87$; OR = 0.90 (CI, 0.47–1.71)] (Table 2).

The results were not modified after adjustment for sex, exposure duration, time to randomization, and baseline carboxyhemoglobin levels (Table 3). Similarly, sensitivity analyses yielded consistent findings when lost to follow-up patients were classified as failures [OR = 0.89 (CI, 0.50–1.60)] or as successes [OR = 0.93 (CI, 0.50–1.71)], and regardless of the method used to treat missing values (Table 3).

Finally, none of trial A patients died or had severe sequels. There was no evidence of a difference at 1 month in the proportion of patients with PNS or DNS between treatment arms.

Trial B

Unexpectedly, of the 170 patients evaluated at 1 month, in the experimental arm (2 HBO sessions), the full recovery rate was significantly lower than in the control arm (47 vs. 68%; $p = 0.007$). This difference remained statistically significant in favor of the control arm, whether lost to follow-up patients were treated as failures or as successes, and after adjustment of prognostic factors (Table 3). Of note, when examining all possible allocations of cases with missing outcome, differences were

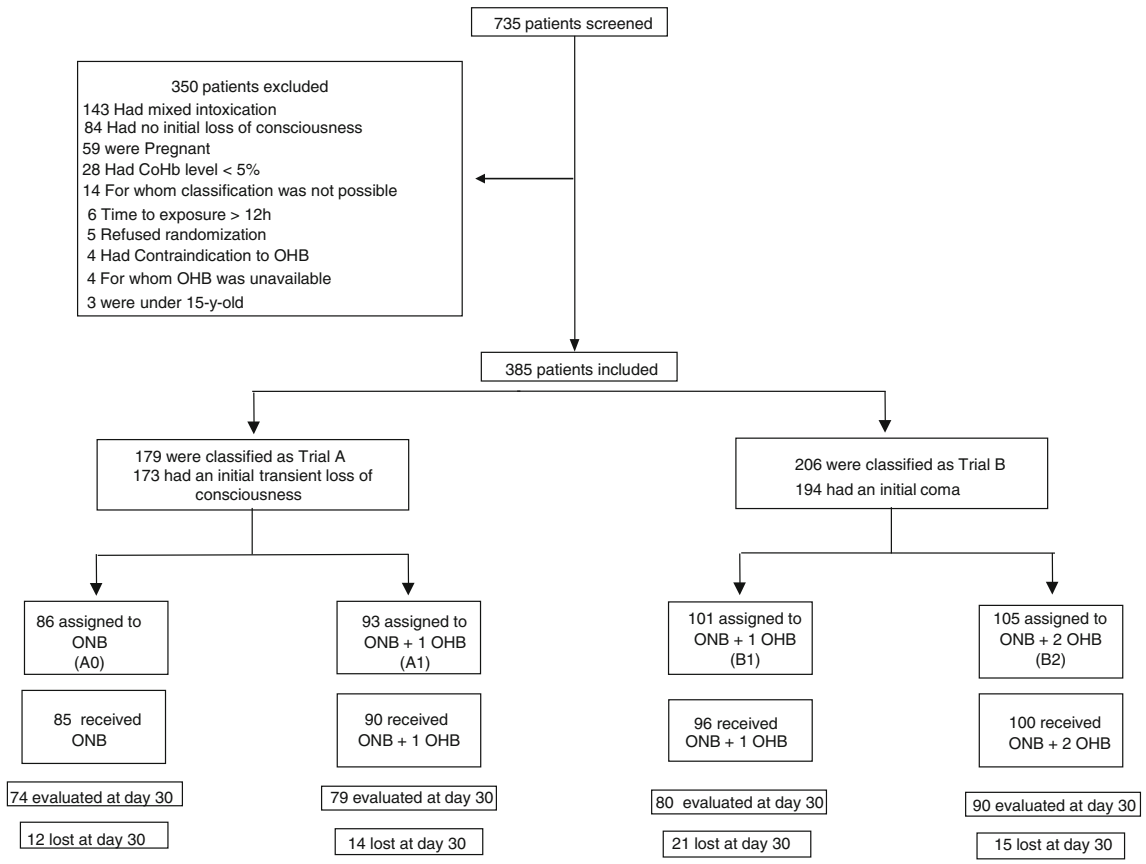

Fig. 1 Trial profile

Table 1 Baseline comparison of randomized patients according to group and randomization arm

Clinical features	Trial A			Trial B		
	A0 ($n = 86$)	A1 ($n = 93$)	p	B0 ($n = 101$)	B1 ($n = 105$)	p
Sex ratio (M/F)	39/47	35/58	0.362	45/56	44/61	0.779
Age[a] (years)	34 (22–50)	32 (23–49)	0.928	38 (28–59)	37 (23–62)	0.620
Proportion poisoned by gas water heater	40/86 (46.5%)	42/93 (45.1%)	0.832	49/101 (48.5%)	51/105 (48.7%)	0.481
Duration of intoxication[a] (h)	4 (1–8)	6 (3–10)	0.073	3 (1–6)	3 (1–10)	0.255
Time to randomisation[a] (h)	4 (3–6)	5 (3–6)	0.381	4 (2–6)	4 (3–5)	0.966
COHb level[a] (%)	22.3 (15.7–30)	20.3 (14.1–27)	0.245	23.3 (15–31.8)	25.5 (19.1–33.3)	0.135
Neurological findings before admission						
Transient loss of consciousness	83/86 (97%)	90/93 (97%)	1.000	11/101[c] (11%)	1/105 (1%)[c]	2.25×10^{-3}
Coma	3/86 (3%)[b]	3/93 (3%)[b]	1.000	90/101 (89%)	104/105 (99%)	2.25×10^{-3}
Other symptoms						
Headaches	72/86 (83%)	76/93 (81%)	1.000	67/101 (66%)	66/105 (63%)	0.557
Gastroenteric dysfunction	48/86 (55%)	48/93 (51%)	0.764	46/101 (45%)	45/105 (43%)	0.778
Seizures	2/86 (2%)	6/93 (6%)	0.280	11/101 (11%)	9/105 (8%)	0.642
Treatment before admission						
Oxygen therapy	78/86 (90%)	88/93 (94%)	0.392	95/101 (94%)	94/103 (91%)	0.313
Mechanical ventilation	0	0	–	4/101 (4%)	11/103 (11%)	0.106
Vascular expansion and/or vasoactive drugs	1/86 (1%)	1/93 (1%)	1.000	4/101 (4%)	7/103 (7%)	0.538
Clinical findings at admission						
Consciousness						
Normal	85/86 (99%)	89/93 (96%)	–	83/101 (82%)	79/105 (75%)	0.417
Confusion	1/86 (1%)	4/93 (4%)	0.37	11/101 (11%)	14/105 (13%)	–
Coma	0	0	–	7/101 (7%)	12/105 (11%)	–
Pulmonary edema	0	0	–	2/99(2%)	4/105 (4%)	0.683

[a] Expressed as medians (25–75th quartile)
[b] Patients mistakenly classified in group A
[c] Patients mistakenly classified in group B

Table 2 Unadjusted comparison of randomized groups in terms of efficacy criteria: evaluation at 1 month

n	Trial A			Trial B		
	A0	A1	p	B1	B2	p
Randomized	$n = 86$	$n = 93$		$n = 101$	$n = 105$	
Lost to follow-up	12 (14%)	14 (15%)	1.00	21 (21%)	15 (14%)	0.27
Assessed	$n = 74$	$n = 79$		$n = 80$	$n = 90$	
Neurological assessment						
Recovered	45 (61%)	46 (58%)	0.869	54 (68%)	42 (47%)	0.007
Moderate sequelae	29 (39%)	33 (42%)	0.869	25 (31%)	42 (47%)	0.043
Deaths	0	0	–	2 (2%)	2 (2%)	1.000
Severe sequelae	0	0	–	0	4 (4%)	0.123
Delayed neurological sequelae	26 (35%)	28 (35%)	1.000	22 (28%)	29 (32%)	0.615
Persistent neurological sequelae	3 (4%)	5 (6%)	0.720	4 (5%)	19 (21%)	0.003
Nature of moderate sequelae						
Asthenia	19 (25%)	28 (35%)	0.222	20 (25%)	37 (41%)	0.033
Headaches	17 (23%)	18 (23%)	1.000	13 (16%)	24 (27%)	0.134
Memory impairment	20 (27%)	14 (18%)	0.176	9 (11%)	23 (26%)	0.019
Disturbed sleep	16 (22%)	15 (19%)	0.693	14 (18%)	21 (23%)	0.348
Difficulties in concentrating	13 (17%)	12 (15%)	0.827	5 (6%)	17 (19%)	0.020
Visual disturbances	7 (9%)	9 (11%)	0.794	6 (8%)	10 (11%)	0.440
Behavioral impairment	7 (9%)	9 (11%)	0.794	4 (5%)	9 (10%)	0.257
Professional outcome						
No resumption of former activity	0	1 (1%)	1.000	1 (1%)	7 (7%)	0.068

Table 3 Comparison of the main end point according to randomization, adjusted effect and sensitivity analysis to assumption for recoding of missing values

Odds ratio [95 CI]; p value	Trial A ($n = 153$)		Trial B ($n = 170$)	
Observed sample: complete case analysis	A0	A1	B0	B1
Recovery rate	61% (45/74)	58% (46/79)	68% (54/80)	47% (42/90)
Unadjusted effect	0.90 [0.47–1.71]; 0.75		0.42 [0.23–0.79]; 0.007	
Adjusted effect	0.92 [0.43–1.97]; 0.84[a]		0.39 [0.19–0.80]; 0.0096[b]	
Recoding missing values: sensitivity analyses				
Allocation to poor outcome				
Recovery rate	52% (45/86)	49% (46/93)	53% (54/101)	40% (42/105)
Unadjusted effect	0.89 [0.50–1.60]; 0.70		0.58 [0.33–1.01]; 0.054	
Adjusted effect	0.85 [0.43–1.66]; 0.63[a]		0.58 [0.31–1.07]; 0.0793[b]	
Allocation to good outcome				
Recovery rate	66% (57/86)	64% (60/93)	74% (75/101)	54% (57/105)
Unadjusted effect	0.93 [0.50–1.71]; 0.80		0.41 [0.23–0.74]; 0.003	
Adjusted effect	1.05 [0.51–2.16]; 0.89[a]		0.38 [0.19–0.74]; 0.0015[b]	
Extreme case favoring control arm				
Recovery rate	66% (57/86)	49% (46/93)	74% (75/101)	40% (42/105)
Unadjusted effect	0.50 (0.27–0.91); 0.02		0.23 (0.13–0.42); 0.0001	
Adjusted effect	0.50 (0.25–1.00); 0.05[a]		0.20 (0.10–0.40); 0.0001[b]	
Extreme case favoring experimental arm				
Recovery rate	52% (45/86)	64% (60/93)	53% (54/101)	54% (57/105)
Unadjusted effect	1.66 (0.91–3.02); 0.10		1.03 (0.60–1.79); 0.91	
Adjusted effect	1.66 (0.84–3.29); 0.15[a]		0.86 (0.47–1.60); 0.64[b]	

[a] Adjusted for sex, duration of intoxication, time to randomization, and initial COHb level
[b] Adjusted for duration of intoxication, time to randomization, coma before and at admission, and initial COHb level

never in favor of HBO therapy (Table 3). Finally, there were more patients with PNS at 1 month in the "two HBO sessions" group (Table 3).

Compliance, adverse events, and change in carboxyhemoglobin level from baseline to treatment completion

In trial A, NBO was stopped prematurely in one patient in the experimental arm because of a panic attack. HBO was stopped prematurely in seven patients in trial B, four in the control arm, and three in the experimental arm because of claustrophobia ($n = 4$), otalgia ($n = 2$), and seizures ($n = 1$). Barotrauma was confirmed for six patients in trial B, four in the control arm, and two in the experimental arm.

Discussion

This study did not confirm that hyperbaric oxygen therapy improves recovery from pure CO poisoning. In addition, in comatose patients, repeating hyperbaric oxygen therapy resulted in worse outcomes compared to one session.

The crude 1-month recovery rate in patients who had experienced only transient loss of consciousness was very similar to previous reports [4]. Severe neurological deficits and death were infrequent regardless of HBO therapy. These findings confirmed the reliability of the definitions discriminating between patients with and without coma. This 'pragmatic' definition was used in a prior randomized trial [4]. When the information was recorded from household members, it may have been imprecise, explaining some misclassifications of patients. Of note, 14/350 patients were excluded because it was not possible to distinguish between loss of consciousness or coma. In comatose patients, the reasons for the observed lower recovery rate and higher risk of neurological deficits with increasing dose of HBO remain unclear. The observed 15% of patients lost to follow was close to the rate reported in most trials [8]. Regardless of the method used to treat missing values, sensitivity analyses never favored HBO treatment. These findings are in line with the higher rate of neurological deficits with HBO reported in another trial of 191 patients, most of whom were suicide attempts [6]. In contrast, a small open-labeled trial found a reduced risk of delayed neurological deficits with HBO (0/30 vs. 7/30; $p < 0.05$) [2]. However, there was major attrition bias with five patients being lost to follow-up and four declining neuropsychological tests. In a trial stopped prematurely for efficacy [7], 6-week cognitive sequels were less frequent with HBO [19 of 76 (25.0%)] than with NBO therapy [35 of 76 (46.1%), $p = 0.007$]. The main difference between this 'positive' trial and our 'negative' trial was the practical modalities for HBO. In the 'positive' study, the HBO-treated group underwent three consecutive sessions, one at a 3 ATA plateau pressure for 60 min and the two subsequent dives at 2 ATA. In our

trial, plateau pressure was limited at 2 ATA as in previous trials [5, 11, 12]. Other remarkable differences between the two studies included different populations (mixed vs. pure CO poisoning), different randomization methods (cluster randomization vs. equal proportion), blinding (double-blind vs. single-blind), and primary outcome measure (complex set of neuropsychological testing vs. self-questionnaire and thorough physical examination). The goal of neuropsychological tests is to detect subclinical abnormalities [13]. We aimed at identifying symptom-free patients. We found a higher rate of minor symptoms than did earlier studies [14, 15], supporting the sensitivity of physical examination by an intensive care physician qualified in neurology. In addition, at 1 month, there were more patients with neurological deficits at physical examination following two HBO sessions than after one session. It is unlikely that neuropsychological testing would have yielded opposite findings. We chose to assess the primary outcome measure at 1 month as most CO-related neuropsychological disturbances commonly developed 7–20 days after CO exposure [16–20].

In summary, in patients with domestic CO poisoning and a transient loss of consciousness (malaise or syncope), one session of hyperbaric oxygen therapy is not superior to normobaric oxygen therapy. In comatose patients, the current trial did not suggest any benefit for two sessions of HBO therapy over one session. Whether HBO therapy at 3 ATA is superior to HBO therapy at 2 ATA requires further study with randomized controlled trials.

Acknowledgments The study was supported by the Assistance Publique des Hôpitaux de Paris. The sponsor had no role in the study design, data collection, analysis, decision to publish, or preparation of the manuscript. Registration numbers were NCT01100515 for trial A and NCT01099995 for trial B. The authors are grateful to the physicians and nursing staff of Raymond Poincaré Teaching Hospital and to Paris area emergency departments for their valuable contribution.

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