Critical Review Form

Therapy

Hyperbaric Oxygen for Acute Carbon Monoxide Poisoning, *NEJM* 2001; 347:1057-1067

Objective: **"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." (p. 1058)**

Methods: **Quadruple-blinded (patient, clinician, outcome assessor, and the statistician) randomized clinical trial from November 1992 through February 1999 at LDS Hospital in Salt Lake City Utah. Inclusion criteria included carboxyhemoglobin level elevation or exposure to ambient CO elevation OR an obvious CO exposure with any of the following symptoms: LOC, confusion, HA, malaise, fatigue, forgetfulness, dizziness, visual disturbances, nausea/vomiting, cardiac ischemia or base excess lower than -2 mmol/L or lactate concentration > 2.5 mmol/L. Exclusion criteria included >24 hours since removal from the CO exposure, age <16 years, unable to obtain informed consent or moribund, or pregnancy.**

In blocks of six, patients were randomized to normobaric oxygen (NBO) or HBO stratified by the presence or absence of loss of consciousness, <6 hours or ≥6 hours interval between of CO exposure and chamber entry, and age (<40 years or ≥ 40 years). The HBO group had three chamber dives within 24 hours based upon a prior retrospective review suggesting that >2 dives are associated with superior neurocognitive outcomes (Gorman 1992). Dive number one was at 3 atmospheres (ATA) then 2 ATA, whereas dives number two and three were at 2 ATA. The NBO group had 15 L/min using a facemask non-rebreather at 1 ATA in the hyperbaric chamber (sham dives).

At the time of enrollment, demographic variables were collected including details of the CO exposure along with a battery of neuropsychological tests: orientation digit span, trail making, digit-symbol, block design, and story recall. This battery was obtained after dives one and three, and at 2- and 6-weeks, and at 6- and 12-months. One of ten psychologists using standardized formats administered these neuropsychological tests in quiet, private examination rooms. After the third dive a repeat, extremely detailed neurological exam was conducted including olfaction, visual acuity, pin-prick, vibratory sensation, forearm pronation-supination, gait,

heel-to-toe gait, and Romberg's test. The follow-up evaluations included the same neuropsych test battery: a questionnaire about CO symptoms, depression, ADL's and general health. Cognitive sequelae was present if the T-score for any neuro subtest was >2 standard deviations below the mean of a normal population or >1 SD if self-reported difficulty with memory, attention, or concentration.

The primary outcome was the incidence of cognitive sequelae at 6 weeks. Secondary outcomes included neuropsychological test scores up to 6 weeks, self-reports of CO symptoms, scores on the depression/ADL general health questionnaires, and neurophysical exam results after the third chamber session. With 100 patients/group the study was designed with 80% power to detect difference in the primary outcome from 5.8% to 18.5% with two-sided alpha = 0.05. The p-value was corrected for multiple comparisons. Multivariable logistic regression was used to adjust the odds ratio for the primary outcome adjusting for stratification and for additional factors associated with both treatment-group assignment and cognitive sequelae.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes. "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." (p. 1058)
2.	Was randomization concealed (blinded)?	Yes. "treatment group assignments were given to respiratory therapists in protected, sequentially numbered, sealed opaque envelopes." (p. 1058)
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "We analyzed the primary outcome according to the intention-to-treat principle." (p. 1059)
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. "Baseline characteristics were similar in the two groups (Table 1), although cerebellar dysfunction before treatment was more frequent in the normobaric oxygen group" (15% vs. 4%, p=0.03) (p. 1060). There was also a significant difference in duration of CO exposure (13 hours in the HBO vs. 22 hours in NBO group).

B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	No. "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 L per minute with the use of a reservoir and a face mask that prevented rebreathing." (p. 1058). Also, "blinding of the patients and the investigators was maintained throughout the study and the data analysis performed at 12 months." (p. 1064) (see Weaver 1994 and Weaver LK et al, *Undersea Hyperb Med* 1997; 24: Suppl:36)
2.	Were clinicians aware of group allocation?	No, see above.
3.	Were outcome assessors aware of group allocation?	No. Ten psychologists (9 PhD candidates) performed neuropsychological testing "all of whom were unaware of the treatment group assignments." (p. 1059). Also, "the statisticians and investigators (for the pre-planned interim analysis) were blinded to patients' treatment group assignment. (p. 1060).
4.	Was follow-up complete?	Yes a total of 5/152 (3%) were lost to follow-up (1 in HBO group, 4 in the NBO group).
II.	**What are the results (answer the questions posed below)?**	

1.	How large was the treatment effect? NOTE: The incidence of cognitive sequelae was higher than in previous research (5.8% HBO vs. 18.5% NBO) despite the fact that mean initial COHg was 25 (both groups) and mean COHg at the start of the chamber dive was 4% (both groups). Cognitive sequelae @ / HBO (%) / NBO (%) / Unadj or (95% CI) / NNT (95% CI) 6 weeks* / 25.0 / 46.1 / 0.39 (0.20-0.78) / 5 (3-22) 6 months / 21.1 / 38.2 / 0.43 (0.21-0.89) / 6 (3.78) 12 months / 18.4 / 32.9 / 0.46 (0.22-0.98) / 7 (4-alpha)	• 76 patients were randomized to each group and the trial was stopped prematurely after the third interim analysis because of significant benefit favoring HBO. • 180 were excluded for various reasons, primarily cost and inconvenience Figure 3 CONSORT diagram p. 1062). • Cognitive sequelae were less likely with HBO at all time intervals. • Mean age of participants was 35 with 12 grade reading level and >70% male. • Suicide was the CO exposure mode in less than 1/3 and headache was the predominant initial complaint (85%). • **HBO was still favored with adjustment for cerebellar dysfunction and stratification variables with OR 0.45 (95% CI 0.22-0.92, P=0.03).** • HBO patients were less likely to complete all 3 dives (18.4% HBO dropped out vs. 3.9% NBO) with reasons to drop out including anxiety, TM rupture, cough, inability to equilibrate middle ear, and non-compliance with return. Nystagmus was more common in HBO (12% vs. 2% p=0.05) • The only two neuropsych subtests to approach significance were the Trail Making Tests A and B and the digit span. • Subjectively HBO patients reported less memory (p=0.004) or attention –concentration problems (p=0.17) • There was no impact of HBO on ADL's, depression, or overall health.

2.	How precise was the estimate of the treatment effect?	See 95% CI above.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Yes, acute symptomatic CO patients with abnormal carboxyhemoglobin levels. Unfortunately, this research does not help with children <16 years, pregnant patients, or treatment delays (>24 hour since CO exposures).
2.	Were all clinically important outcomes considered?	Yes, including subjective symptoms and functional limitation for up to one-year.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain since the design was underpowered to evaluate risk, did not assess costs, and only had a mean delay of 4 hours before hyperbaric chamber treatment ensued after the first COHg level. Many rural settings would have difficulty matching this speed.

Limitations

1) **Exclusion of pregnant, children, and moribund patients.**

2) **Uncertain sensitivity/specificity of neuropsych battery since the Messier paper did not assess diagnostic accuracy or report a criterion standard for abnormal post-CO cognitive dysfunction.**

3) **Failure to evaluate or even contemplate the cost-effectiveness implications.**

4) **Significant number of patients refusing randomization (with no statistical assessment of this population) limiting external validity.**

5) **Premature closure of the trial.**

Bottom Line

Treatment of non-pregnant adult patients suffering from acute (less than 24-hours since removal from the source) symptomatic CO toxicity with three HBO sessions within 24 hours reduces the negative cognitive sequelae at 6 weeks and 12 months with NNT 5 and 7, respectively. The most sensitive neuropsych subtests are the Trails A, Trails B, and digit span tests. Future trials are needed to verify the accuracy and reliability of these neuropsych tests, as well as the cost-effectiveness of HBO in various subsets of patients. In addition, appropriately powered HBO safety trials are needed.