Critical Review Form

Therapy

Delayed Neuropsychologic Sequelae After Carbon Monoxide Poisoning: Prevention by Treatment With Hyperbaric Oxygen, *Ann Emerg Med* 1995; 25:474-480

Objective: **"To assess the incidence of DNS (delayed neuropsychologic sequelae) after CO (carbon monoxide) poisoning and to determine whether the incidence of DNS was different between groups treated with ambient pressure oxygen or HBO." (p. 475)**

Methods: **Single-center, unblended, prospective randomized trial of HBO and normobaric oxygen therapy. Between September 1989 and December 1993 eligible CO poisoning patients referred to the University of Pennsylvania Institute for Environmental Medicine were enrolled. Inclusion criteria were history of acute exposure to combustion products, increased carboxyhemoglobin (COHb) levels not explained by smoking status, and the presence of CO symptoms (headache, nausea, lethargy, confusion, or obtundation). Exclusion criteria included cardiac compromise (chest pain or abnormal ECG) or a history of unconsciousness. All enrolled subjects received a "standard physical exam", COHg level, and chest x-ray.**

The treatment group received HBO at 2.8 atmospheres pressure (ATA) for 30 minutes then 2.0 ATA for 90 minutes. The control group received 100% oxygen (normobaric oxygen = NBO) through a non-rebreather facemask until all symptoms resolved. In all cases, HBO began within 6 hours of removal from the CO source. Immediately after completion of oxygen therapy all patients had a validated neuropsychological battery of tests administered (Messier 1991): General orientation, Digit Span, Trial Making, Digit Symbol, Aphasia Screen, and Block Design. These cognitive tests were administered in a quiet corner of the ED or in the hyperbaric chamber.

Patients were instructed to contact research staff (available 24/7) if they experienced any abnormal symptoms following their HBO or NBO therapy. These symptomatic patients were examined, usually in their homes. All patients were interviewed for symptoms at one-week, had repeat neuropsychologic testing at 3 to 4 weeks, and were re-interviewed via telephone at 3-months.

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 though the method of randomization (even-odd, envelope) was not detailed.
2.	Was randomization concealed (blinded)?	No, this was unblinded and potentially biased.
3.	Were patients analyzed in the groups to which they were randomized?	No, there was no mention of intention-to-treat.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes, as detailed in Tables 1-2 (pp 475-476) "patients in the two treatment groups were similar" for age, COHb, education, co-morbid illnesses, initial symptoms, and delay until oxygen therapy ensued. In addition, the "neurologic status after oxygen treatment was not discernibly different between groups." (p. 477)
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?	Yes, this was an unblinded study. Multiple potential biases including expectation bias, attention bias and ascertainment bias. (Sackett 1979)
2.	Were clinicians aware of group allocation?	Yes, this was an unblinded study. The authors justify the unblinded design "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." However, they would not have had to "dive" patients – just putting patients into the chamber and pumping it with normobaric 100% oxygen would have fooled most patients and clinicians without exposing the patients to any undue risk (see Weaver 1994 and Weaver LK et al, *Undersea Hyperb*

		Med 1997; 24: Suppl:36).
3.	Were outcome assessors aware of group allocation?	Yes, hence potential for ascertainment bias.
4.	Was follow-up complete?	No, 9/65 (14%) were lost to follow-up including "two patients in each treatment group refused neuropsychologic retesting but denied symptoms of DNS during telephone interviews conducted over the next 3 months." (p. 477) Also two patients in the NBO and three patients in the HBO group were lost to follow-up (NNT=5, 95% CI 5-26)
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• 65 enrolled (32 randomized to NBO, 33 to HBO) • DNS symptoms developed in 8 NBO patients and none of the HBO patients, but only seven had concurrent deterioration in at least one subtest category. The incidence of DNS was 23% (95% CI 8.2% - 38.4%). • Deterioration in neuropsych testing occurred in only three subtests: Trail Making, Digit Symbol, and Block Design. • Risk for developing DNS could not be established using age (DNS 46 years vs. 37 years mean age), COHb level (19% vs. 20%), or duration of CO exposure. • DNS persisted for a mean of 41^{+} 8 days. • Three of seven DNS patients had their activities of daily living impaired by their symptoms.
2.	How precise was the estimate of the treatment effect?	See 95% CI above. The authors do not provide any estimates of precision.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	

1.	Were the study patients similar to my patient?	Probably, since most acute CO poisoning patients go to an ED, although this study's population may be a subset of ED CO patients since they were referred to an HBO chamber which we lack at our institution (spectrum bias).
2.	Were all clinically important outcomes considered?	Yes, including HBO side effects, DNS-related symptoms, symptom duration, and impact of DNS symptoms of functional status. It would also be beneficial to assess symptom severity and the costs associated with HBO.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain about the potential harms of HBO since the authors did not provide any systematic method to ascertain harms nor did they power their study to identify harms. No cost-estimates were provided.

Limitations

1) **No details on randomization method.**

2) **No assessment of oxygen therapy duration before HBO was initiated.**

3) **No *a priori* or *post hoc* power calculation.**

4) **Potential alpha inflation since multiple testing performed without adjusting alpha level.**

5) **No statement of intention to treat.**

6) **No CONSORT diagram.**

7) **Insufficient description of the outcome assessment. Who conducted the neuropsych testing? How were these individuals trained? How were the activities of daily living assessed?**

8) **Unblinded trial. A sham hyperbaric exposure (no dive) would have been ethical and feasible.**

Bottom Line

Small single center trial of acute CO poisoning patients demonstrating that HBO (2.8 ATA x 0.5 hours then 2.0 ATA x 1.5 hours) is superior to NBO with NNT = 5. This unblinded trial has a high likelihood of bias and the authors appropriately suggest that additional studies are needed before wide spread use of HBO for CO poisoning. Future authors should use a similar definition of DNS, assess trial power *a priori* while incorporating costs and transport times (to HBO chamber) into a triple blinded RCT.