Critical Review Form

Therapy

Hyperbaric oxygen therapy for acute domestic carbon monoxide poisoning: two randomized controlled trials, *Intensive Care Med* 2011; 37:486-492

Objective: **To compare "NBO (normobaric oxygen) and HBO (hyperbaric oxygen) in patients with transient loss of consciousness, and in comatose patients, NBO with one or two HBO sessions." (p. 487)**

Methods: **Two parallel group randomized controlled trials conducted between October 1989-January 2000 at Raymond Poincare' Teaching Hospital (Garches, France). Patients were age >15 years and admitted for domestic CO exposure within 12 hours of the exposure. Diagnosis was based on a carboxyhemoglobin level >10% (smoker) or >5% (non-smoker) using a spectrophotometer in conjunction with a compatible history and/or "tests conducted by public health service to measure CO production at home." (p. 487) The exclusion criteria included: mixed poisoning (CO plus another drug), suicide attempt, pregnancy, HBO contraindications (PTX or circulatory collapse), technical obstacles to HBO, normal consciousness, non-domestic CO poisoning, difficulty establishing initial loss of consciousness or coma; and consent refusal.**

The two trials were labeled A and B with A_0 and B_1 the control arms and A_1 and B_2 the experimental treatment arms.* Trial A were those with transient LOC where as trial B were those with a coma. A_0 was 6 hours of NBO, A_1 was 4 hours of NBO and one HBO session, B_1 was 4 hours of NBO and one HBO session (same as A_1) and B_2 was 4 hours of NBO and two HBO sessions (separated by 6- to 12-hours). NBO was delivered as 100% FiO_2 through a facemask or mechanical ventilation. Each HBO session was in a multiplace chamber with 30-minutes for compression , 1-hour at 2 atmospheres pressure (ATA), and 30 minutes decompression. Diazepam (10 mg IM) was administered before each HBO session to prevent oxygen-induced seizures.

At 1-hour subjects completed a subjective questionnaire to identify symptomatic sequelae of CO poisoning: headaches, tiredness, memory difficulty, problems concentrating or sleeping, visual disorders, or any new difficulties with social or professional activities. A detailed physical exam was performed by an

intensive care physician at the ICU outpatient clinic. The primary endpoint was complete recovery (defined below), while secondary endpoints included 1-month rates of persistent neurological sequelae, delayed neurological sequelae, and the proportion of patients who resumed their former occupational activity. The authors reported two power analyses. Trial A required 245 patients per arm to detect a 15% recovery rate difference with 90% power and a two-sided alpha of 0.05. Trial B required 240 patients per arm to detect a 15% difference with 90% power with a two-sided alpha of 0.05. Therefore, the total number of patients required was 490 + 480 = 970. The adjusted odds ratios with 95% CI were computed from logistic models to estimate the strength of the association between the randomly allocated treatment and the complete recovery rates. The p-values were adjusted to 0.029 for the multiple comparisons of the interim analysis.

Definitions

Complete recovery – absence of symptoms on self-assessment questionnaire with a normal physical exam

Moderate sequels – one or more symptoms on the self-assessment questionnaire with a normal physical exam.

Severe sequels – any objective abnormalities at patient's exam.

Coma – GCS <8, but the authors do not describe when this assessment occurred.

Transient loss of consciousness, malaise, syncope – normal consciousness at the time of rescue and amnesia or reported loss of consciousness.

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 randomized (1:1) by using numbered sealed envelopes. An independent statistician prepared a computer-generated allocation sequence for each trial (A and B)." (p. 487)
2.	Was randomization concealed (blinded)?	No. There is no clear statement of blinding of patients or clinicians (no sham dives). However, outcome assessors were blinded (see below).
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "Statistical analysis was performed on an intention-to-treat basis." (p. 488)
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes, there are no statistically significant differences between the treatment groups in either trial with the exception of transient LOC and coma which were both significantly more likely in B_2 than B_1 (Table 1 p. 490)
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, so there was an increased likelihood of recall bias.
2.	Were clinicians aware of group allocation?	Yes, so there was an increased likelihood of co-intervention bias.
3.	Were outcome assessors aware of group allocation?	No. "They underwent a thorough physical examination at the ICU outpatient clinic by one intensive care physician qualified in neurology who remained blinded to patient's treatment arm." (p. 488)
4.	Was follow-up complete?	No, the lost to follow-up rates were 12/86 (14%) for A_0, 14/93 (15%) for A_1, 21/101 (21%) for B_1, and 15/105 (14%) for B_2.

II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• After enrolling 385 total patients, the trial was terminated prematurely after the pre-planned interim analysis showed **likely harm in trial B and no benefit in trial A**. • In trial A the complete recovery rates were 61% control arm and 58% in the experimental arm. None of these patients died. • In trial B the complete recovery rates were 47% after two HBO treatments versus 68% (p=0.007) after one. • **The results for trial A were not changed when adjusted for sex, exposure duration, time to randomization, or baseline carboxyhemoglobin level or when lost to follow-up were classified as failures (OR = 0.89, 95% CI 0.50-0.60) or as successes (OR 0.93, 95% CI 0.50-1.71).** • Similarly, "when examining all possible allocation of cases with missing outcome, differences were never in favor of HBO therapy." (p. 491) • HBO was stopped prematurely for the following side effects: claustrophobia (n = 4), otalgia (n = 2), seizures (n = 1).
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?	Uncertain. How was "domestic" CO exposure defined and by whom? Were these patients recruited from an ED or ICU? What are the patient's race, educational level, baseline neurocognitive status, and co-morbid illness burden?
2.	Were all clinically important outcomes considered?	No, although the authors' secondary outcomes included functional status, they did not report these outcomes specifically (just a general statement about no influence of intervention on secondary outcomes).
3.	Are the likely treatment benefits worth the potential harm and costs?	No, based on the current data HBO offers no benefit to NBO in acute domestic CO poisoning and may be harmful.

Limitations

1) **Why did it take >10 years to report this trial data?**

2) **Unblinded to patients/clinicians so potential for recall bias and co-intervention bias.**

3) **Injection of diazepam could have biased results since only HBO subjects received this intervention.**

Bottom Line

For domestic CO poisoning there is no benefit of HBO over NBO. In comatose CO poisoning patients, two sessions of HBO may provide worse outcomes than one session.