Critical Review Form
Meta-analysis

HBO for CO poisoning, *Cochrane Reviews* 2011, Issue 4 Art No: CD 002041

Objective: **"To examine the efficacy of HBO in reducing the prevalence of neurologic signs and symptoms approximately 4 to 6 weeks following treatment in patients with acute CO poisoning." (p. 5)**

Methods: **Electronic search of multiple sources (see I-2 below) by the Cochrane Injuries Group through June 2010 for randomized controlled trials of non-pregnant adults with acute carbon monoxide poisoning which reported the frequency of neurological sequelae at one-month. Two reviewers abstracted the individual trials' distributions for the following data from eligible trials: age, gender, CO level at the time of randomization, and history of loss of consciousness, in addition to the intervention (duration and dose of HBO or NBO) and the presence of signs/symptoms during follow-up. Individual trial quality was assessed for bias using methods described by Higgins et al (see I-3 below). The authors did not assess for publication bias and formal statistical assessment of heterogeneity was not possible due to the small number of studies. (p. 7) A random effects model was used for pooled analysis. Subgroup analyses by severity, intent, and duration of poisoning were not possible.**

Guide	Question	Comments
I	***Are the results valid?***	
1.	Did the review explicitly address a sensible question?	Yes, does HBO (which is expensive, not readily available, and exposes patients to additional risk including barotrauma, seizures, pulmonary edema, and claustrophobia) effective to reduce neurological symptoms four weeks following CO poisoning.
2.	Was the search for relevant studies details and exhaustive?	Yes, the investigators searched the Cochrane Injuries Group Register, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, Pub Med, and Web of Science (Science Citation Index and Conference Proceedings Citation Index) using a variety of search terms (see Appendix 1).

3.	Were the primary studies of high methodological quality?	No, "all included trials were at considerable risk of bias" including four with no or minimal blinding, multiple analyses without statistical adjustment, and high lost-to-follow-up rates. Study quality was assessed on the following parameters: • Was there adequate sequence generation? • Was allocation adequately concealed? • Were incomplete outcome data adequately addressed? • Are reports of the study free of suggestions of selective outcome reporting? • Was study free of other problems that could put it at risk of bias?
4.	Were the assessments of the included studies reproducible?	Unknown. The authors use the Higgins quality assessment system, but they do not provide any measures of article quality assessment reproducibility between raters.
II.	***What are the results?***	

1.	What are the overall results of the study?	• Six trials of 1335 patients randomized to either HBO or NBO were included, although one was an abstract which has never undergone peer-reviewed publication since 1996 and the authors of this 1996 abstract never responded to Cochrane requests for more details. • The prevalence of persistent signs/symptoms of CO poisoning at 4-6 weeks pooled among all six trials was 29% HBO vs. 34% NBO (Odds Ratio 0.78; 95% CI 0.54-1.12), but no universal description or measurement instrument for persistent neurologic sequelae or delayed neurologic sequelae were used. The potential biases of the individual trials are summarized below: **Raphael 1989 and Annane 2010** (486 patients) - found no benefit but excluded severe CO poisoning (Type II error) **Thom 1995** (60 patients) - first published trial to claim HBO benefit - outcome assessment by unblinded clinicians - failure to adjust analysis for multiple comparisons (interim analysis) - premature termination **Mathieu 1996** (575 patients) - never published, reported as interim analysis - difference noted at 3-months but not 1-month or 6 months and lack of adjustment for multiple comparisons **Scheinkestel 1999** (88 patients) - only negative study to include sham intervention - 54% of subjects randomized to treatment were lost to flu @ 4 weeks. **Weaver 2002** (152 patients) - only positive study to include sham intervention - changed original endpoint from delayed neurologic sequelae in 1995 to all neurologic sequelae in 2002. - the primary determinant of statistically significant differences between groups were non-specific symptoms. - premature termination of the trial

2.	How precise are the results?	See the Odds Ratio 95% CI above.
3.	Were the results similar from study to study?	Yes, 4 trials showed no difference and 2 trials showed benefit (I^2 = 46%)
III.	***Will the results help me in caring for my patients?***	
1.	How can I best interpret the results to apply them to the care of my patients?	Although there is no conclusive data for pregnant patients or severe CO poisoning (both populations excluded in this meta-analysis), HBO cannot be recommended for the treatment of CO poisoning. Contrary to some voices in the HBO community (Stoller 2007, Weaver 2009, Logue 2008), clinical equipoise still exists to justify further RCT's to assess HBO effectiveness for acute CO poisoning (Wolf 2008, ALS Guidelines 2010, Vanden Hoek 2010).
2.	Were all patient important outcomes considered?	No, this review did not assess the severity or duration of neurological symptoms or the resulting functional limitation.
3.	Are the benefits worth the costs and potential risks?	No, the costs do not out-weigh the benefits since no benefits are apparent.

Limitations

1) **No assessment for publication bias.**

2) **No standard and reproducible definition for "neurologic sequelae".**

3) **No report of quality assessment reproducibility.**

4) **Insufficient data for subgroup analysis (age, pregnancy, severity of exposure, etc.**)

5) **No assessment of harm (HBO adverse events).**

Bottom Line

HBO cannot be routinely recommended for acute CO poisoning. Compared with NBO, HBO is more expensive, not readily available, and associated with adverse reactions including barotrauma, seizures, pulmonary edema, and claustrophobia.

Sufficient clinical equipoise exists to justify future RCT's that are triple-blinded (investigator, patient, outcome assessor) using sham dives, using explicit and reproducible primary and secondary outcome measures defined before recruitment ensues. Unfortunately, a review of clinicaltrials.gov reveals no such registered trials currently underway.