

The Cochrane Library – Feedback

Hyperbaric oxygen for carbon monoxide poisoning

DN Juurlink, NA Buckley, MB Stanbrook, GK Isbister, M Bennett, MA McGuigan

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Christopher Logue

Date received: November 27, 2006

Cite this comment as: <http://www.cochranefeedback.com/cf/cda/citation.do?id=9585#9585>

To the Editor:

In his brief and incomplete response, Dr. Juurlink suggests that I deliberately neglected to provide a conflict of interest statement to accompany my feedback comments. He also provides an ominous warning to anyone else who dares to add feedback commentary challenging the methods or conclusions of this Cochrane Report. To clarify for the benefit of the readers of this forum, no one can provide feedback commentary to the Cochrane Library without providing a conflict of interest statement. I did provide such a statement with my comments on October 6th, however, due to computer error the statement did not appear when my comments were posted. Since that time, the computer error has been corrected and my conflict of interest statement now appears with my posting. I am surprised that Dr. Juurlink is unaware of how the Cochrane feedback process works. Dr. Juurlink might improve his credibility if he focused on the content of the feedback rather than making inaccurate assumptions about the behavior of others. I also feel it would be beneficial if Dr. Juurlink could clarify any misunderstandings of his earlier posts in this forum.

My commentary was limited to a discussion regarding the methods of this particular Cochrane Report. Although I did not provide any statement with regards to my personal beliefs, I thank Dr. Juurlink for doing this for me. I fear, however, that Dr. Juurlink may be missing the point of my feedback response. In the world of evidence based medicine personal beliefs are entirely irrelevant. Evidence based medicine is about the systematic, objective, thorough and conscientious review of the existing medical literature.

I have read many Cochrane Reviews in the past. However, this is the first one that I have come across that has included two separate accusations of academic dishonesty.

#1) With regards to the discussion of the Thom et al trial (1995).

Due to creative interpretation of a single sentence from an interim report (1), the Cochrane authors claim that in 1992 Thom et al had enrolled 58 patients into their trial. At that time there were no statistically significant results. The Cochrane authors then claim that over the next three years, Thom et al only added an additional seven patients before stopping the trial early because the results were statistically significant. They claim that the addition of these seven patients happens to be in the precise distribution to make the results significant. They go as far as performing a Fisher's exact test for this scenario. Readers of the Cochrane Review are left to come to one of two conclusions regarding this discussion; 1) This type of behavior by an investigator is irregular and highly suggestive of academic dishonesty or 2) Somehow the Cochrane authors are wrong.

In fact, in 1992 Thom et al had enrolled 27 patients into the trial (the Cochrane authors doubled the number then added an additional four patients). The original data remains on file here at the University of Pennsylvania and is available to anyone who wishes to access it. It appears that the Cochrane authors were comfortable making this accusation without checking the data and verifying their odd conclusion.

The Cochrane authors have since publicly admitted their error in a separate forum (2). However, the Cochrane Collaboration has yet to print a retraction or correct the error.

#2) We are now discussing the second accusation of academic dishonesty from this Cochrane Report. The claim is that the original intended primary outcome measure changed in the Weaver et al trial (2002) in order to "shed a favorable light" on hyperbaric oxygen therapy for the treatment of CO poisoned patients.

The primary outcome measure of a trial is determined at the time the trial is designed and is defined in the original study protocol that gets submitted to the IRB for approval. The Cochrane authors claim that DNS was the original intended primary outcome measure. It is difficult to make this claim when the investigator admits in an editorial referenced by Dr. Juurlink that DNS was not defined until the trial was well underway. In addition, Dr. Juurlink provides references that specifically discuss the type of error he claims Weaver et al made (3,4,5). Unfortunately, the Cochrane authors used none of the techniques outlined in these references. It also would have made sense for the Cochrane authors to make an attempt to access the study protocol. By doing this, they could have either verified their assumption or saved themselves the trouble of a defense in this forum.

The Cochrane authors, again, felt comfortable making this accusation without utilizing accepted techniques for proving such a claim or attempting to verify their conclusions by accessing the original study protocol.

As a practicing Emergency Medicine and Hyperbaric Medicine physician who frequently stands at the "coal face", it is my job to stay up-to-date with all of the medical literature with regards to this topic. As such a physician, I am keenly aware that controversy continues to exist regarding the use of hyperbaric oxygen therapy for CO poisoned patients. I also am aware of the probability that a separate panel of experts may come to a similar final conclusion as this Cochrane Review. However, I doubt that a separate panel of experts would make similar accusations of academic dishonesty without thoroughly verifying the facts first. In the world of evidence based medicine the end does not justify the means. It is for this reason that I respectfully request that a separate panel of experts be convened to review this topic.

Sincerely,

Christopher Logue, MD
Health Systems Clinician
Department of Emergency Medicine
The University of Pennsylvania School of Medicine

- 1) Thom SR, Taber RL, Mendiguren IL, Clark JM, Fisher AB. Delayed neurological sequelae following CO poisoning and the role of treatment with 100% O2 or hyperbaric oxygen- A prospective randomized, clinical study. Undersea Biomedical Research 1992; 19 (Suppl): 47.
- 2) Juurlink, DN. Hyperbaric Oxygen for Carbon Monoxide Poisoning – Evidence versus Opinion. Toxicol Rev 2005; 24 (3): 159-160.
- 3) Chan AW, Krleza-Jeric K, Schmid I, Altman DG. Outcome reporting bias in randomized trials funded by the Canadian Institutes of Health Research. CMAJ 2004; 171(7):735-740.
- 4) Chan AW, Hrobjartsson A, Haahr MT, Gotzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. JAMA 2004; 291(20):2457-2465.
- 5) Chan AW, Altman DG. Identifying outcome reporting bias in randomised trials on PubMed: review of publications and survey of authors. BMJ 2005; 330(7494):753.

Conflict of Interest:

I serve as an Emergency Medicine and Hyperbaric Physician at the University of Pennsylvania. I am paid a yearly salary and provide emergency coverage for the Hyperbaric Medicine Program after-hours occasionally. My employment contract states that I do not receive additional pay for covering this call or for responding to emergency hyperbaric oxygen therapies (this can be provided if necessary). I am often directly involved in caring for patients with CO poisoning but do not personally benefit financially from this service. In addition, the facility at which I work loses tens-of-thousands of dollars yearly directly related to the cost of treating CO poisoned patients emergently.

David Juurlink

Date received: October 9, 2006

Cite this comment as: <http://www.cochranefeedback.com/cf/cda/citation.do?id=9571#9571>

In response -

Despite their prolixity, Dr. Logue's comments offer no new insights on this matter. Indeed, some of his comments seem to reflect a misunderstanding of my earlier posts in this forum.

This is not the first time our review has been criticized by a hyperbaric medicine physician, and it will likely not be the last.

I understand the inclination of hyperbaric physicians to 'believe in' and defend the therapy. However, I encourage any subsequent contributors to this debate to declare their potential conflicts - professional, reputational, or financial - so that readers may interpret the feedback in context.

Sincerely,

David Juurlink, MD, PhD, FRCPC
University of Toronto

Christopher Logue

Date received: October 6, 2006

Cite this comment as: <http://www.cochranefeedback.com/cf/cda/citation.do?id=9569#9569>

Feedback with regards to the Cochrane Review "Hyperbaric Oxygen for Carbon Monoxide Poisoning".

To the Editor:

The authors of the Cochrane review argue that the Weaver et al trial published in the New England Journal of Medicine suffers from a single fatal flaw which renders the results insignificant. They claim that the original intended primary outcome of the trial was changed from trial inception to final publication. They claim the original intended primary outcome was delayed neurological sequelae, not the outcome that is published in the NEJM publication: six week neurological sequelae.

Dr. Juurlink provides references that discuss this type of error in his response to Weaver in the Cochrane feedback webpage (1,2,3). Having read these documents in detail, I respectfully disagree that there is evidence that the primary outcome in the NEJM trial changed from trial inception to final publication. According to these references, the Cochrane authors simply do not present sufficient evidence to support their claim.

As a brief summary to bring readers up to speed...the first two articles (1,2) discuss this type of error by comparing study protocols to final published reports. In this discussion Chan et al point out that although selective reporting of or changes in outcome measures seems to occur frequently in trials, these types of errors are difficult to prove. They point out that the only definitive way to prove such a claim is to compare the original study protocol to the final publication and they recommend that all study protocols should be available in publishable format to combat these types of errors in the future. Weaver et al began their trial in 1992, before there were centralized sites for registering randomized trials. Therefore, it is impossible to perform this type of analysis as recommended by Chan et al.

There is, however, an alternative way to identify whether unreported or changed outcomes occurred in a particular trial if the study protocol is not available for comparison to the final publication. Chan et al outline in detail the methods that should be used in their third article (3). For each trial Chan et al identified the primary and any subsequent publications to extract the number and characteristics of reported outcomes. They then identified unreported or changed outcomes if they appeared in the methods section but not the results section of any publication. They also surveyed the investigators.

Having read these articles there are several problems associated with Dr. Juurlink's assertion that the original intended primary outcome changed for the NEJM trial.

1) No where in any of the articles by Chan et al is there any mention of or recommendation for the use of editorial comments as definitive proof that this type of error has occurred. An editorial does not possess a methods and a results section for analysis. In addition, the Cochrane authors did not employ any of the techniques outlined by Chan et al to provide evidence that the primary outcome changed in the trial.

2) Although the Cochrane authors insist that this type of error did occur, they made no effort to access the original study protocol. In this regard it is notable that they did make an effort to obtain unpublished data from the Scheinkestel et al trial to support the notion that hyperbaric oxygen therapy is not beneficial for the treatment of CO poisoned patients.

3) In his response, Dr. Juurlink quotes an editorial written by Weaver:

"During the course of the trial, it became evident that operational definitions of DNS and PNS were needed"

If an operational definition of DNS did not exist at the time the study protocol was written, then it stands to reason that this was not the original intended primary outcome and it will not appear in the original study protocol and procedures. This directly contradicts assertions by the Cochrane authors. In light of this fact, it is highly probable that neurological sequelae measured at six weeks (as described in the methods and results section of the trial) was the original intended primary outcome measure. At most the Cochrane authors can assert that Weaver et al. appeared to be interested in DNS (as specifically defined during the course of the trial) as a later, secondary outcome measure from the referenced editorial comments.

The Cochrane authors have since admitted to at least two other errors in their review: 1) Misinterpretation with lack of fact checking of an interim report resulting in erroneous criticism of the Thom et al trial. 2) The Scheinkestel et al trial did not belong in the Cochrane review as the outcome measure was neurological sequelae at the end of treatment, not at a time 4-6 weeks later.

Dr. Juurlink has responded to commentary in this feedback website on several occasions. These responses indicate that he remains resistant to criticism and steadfast in defending the Cochrane Report regardless of mounting errors and inconsistencies.

In light of the errors that have been outlined and legitimate disagreement with the assertion that the primary outcome measure changed in the NEJM trial, I respectfully request that a separate panel of experts be convened by the Cochrane Collaboration to review this topic. It would seem desirable to include at least one individual demonstrating published expertise with regard to the pathophysiology of CO poisoning.

Sincerely,

Christopher Logue, MD
Health Systems Clinician
Department of Emergency Medicine
University of Pennsylvania School of Medicine

1) Chan AW, Krlaza-Jeric K, Schmid I, Altman DG. Outcome reporting bias in randomized trials funded by the Canadian Institutes of Health Research. CMAJ 2004; 171(7):735-740.

2) Chan AW, Hrobjartsson A, Haahr MT, Gotzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. JAMA 2004; 291(20):2457-2465.

3) Chan AW, Altman DG. Identifying outcome reporting bias in randomised trials on PubMed: review of publications and survey of authors. *BMJ* 2005; 330(7494):753.

Conflict of Interest:

I serve as an Emergency Medicine and Hyperbaric Physician at the University of Pennsylvania. I am paid a yearly salary and provide emergency coverage for the Hyperbaric Medicine Program after-hours occasionally. My employment contract states that I do not receive additional pay for covering this call or for responding to emergency hyperbaric oxygen therapies (this can be provided if necessary). I am often directly involved in caring for patients with CO poisoning but do not personally benefit financially from this service. In addition, the facility at which I work loses tens-of-thousands of dollars yearly directly related to the cost of treating CO poisoned patients emergently.

David Juurlink

Date received: October 3, 2006

Cite this comment as: <http://www.cochranefeedback.com/cf/cda/citation.do?id=9566#9566>

In response,

Rational people may reach different conclusions when faced with the same information, depending on their perspective. Our goal has always been to critically appraise the available evidence on a therapeutic intervention that remains one of the most important unresolved issues in clinical toxicology.

Rather than engage in another point-by-point rebuttal to Dr. Weaver, I wish only to make a few observations.

For clinicians at the 'coal face' who ask the question "Should my patient with carbon monoxide poisoning be treated with hyperbaric oxygen?" the only honest answer is "No one really knows for sure." Much of the existing literature on this topic is highly polarized or written by strong proponents of HBO, and is therefore of limited utility for clinical decision making.

The available evidence can be summarized as follows: As an intervention, HBO is costly and carries risk. It is possible that HBO may improve neurologic outcomes in some patients with carbon monoxide poisoning, but it is not clear who those patients are, what the magnitude of any beneficial effect might be, or in which patients the potential benefits of therapy might justify both the risks and costs.

We now sit almost two decades after the publication of the first randomized trial of HBO for carbon monoxide poisoning. Dr. Weaver and his colleagues have made an important contribution to the literature, but their study alone is insufficient to guide practice for the reasons outlined in our review and most recent response in this forum. In the absence of conclusive evidence, thousands of patients with CO poisoning have either received or gone without a treatment that might be helpful, could be ineffective, or may be harmful, depending on the setting.

In summary, there is both an urgent need and ample justification for a multicentre randomized controlled trial on the efficacy of HBO for carbon monoxide poisoning. Dr. Weaver has issued a call for multicentre collaboration previously.(1) It appears that on this point, at least, we might agree.

Sincerely,

David Juurlink, MD, PhD, FRCPC

References

(1) Weaver LK, Hopkins RO, Larson-Loehr V. Carbon monoxide poisoning: a review of human outcome studies comparing normobaric oxygen with hyperbaric oxygen. *Ann Emerg Med* 1995; 25(2):271-272.

Lindell Weaver

Date received: September 26, 2006

Cite this comment as: <http://www.cochranefeedback.com/cf/cda/citation.do?id=9563#9563>

Dear Editor:

I appreciate Dr. Juurlink's response to my comments regarding his review of hyperbaric oxygen for carbon monoxide poisoning. Also, I thank Dr. Juurlink for upgrading the allocation concealment of our trial to an "A" rating. I will attempt to offer readers of this review additional insight into our trial and my previous comments.

The sensitivity analysis offered by Dr. Juurlink implies that all the randomized trials investigating hyperbaric oxygen for CO poisoning are equivalent, and of course, they are not, a point the Cochrane Review authors have conceded. Only two randomized trials enrolled all patients, including those with severe poisoning (1,2). I argued that Scheinkestel, et al's trial (1) should be omitted from consideration in this analysis because one-month outcomes are not reported, a requirement for inclusion set by the review authors. This leaves our trial as the only trial that enrolled severely poisoned patients (2). A sensitivity analysis is therefore unnecessary, since we showed efficacy of hyperbaric oxygen for acute CO poisoning (2).

Dr. Juurlink is incorrect about the lack of a Data and Safety Monitoring Board (DSMB) for our study. Our hospital's IRB agreed to serve this role. I agree we should have registered our clinical trial. However, at the time we conducted our trial, registration was not available.

Contrary to Dr. Juurlink's contention, cognitive outcomes are meaningful, and numerous trials have clearly demonstrated this, a point we have discussed previously (3). Dr. Juurlink again argues that because the group mean data appear normal, these patients must not be impaired. As I explained in my prior response, as well as elsewhere (3), the group mean neuropsychological data includes both the patients with cognitive sequelae and those patients without cognitive sequelae, whose scores have been influenced by practice effects, since all patients took these tests 3 times prior to the 6-week assessment. In fact, the magnitude of sequelae in those patients with cognitive dysfunction is dramatic (3).

Dr Juurlink maintains that we changed our definition for cognitive sequelae, even suggesting that professional dishonesty is at play. I have discussed this issue in my prior rebuttal to the Cochrane Review. We did all analyses prior to treatment allocation disclosure, so the idea that we fit the results to some preconceived notion that hyperbaric oxygen was favorable is ridiculous and offensive.

I think it unlikely that anything further I could offer in this forum would persuade Dr. Juurlink and other authors of this review that hyperbaric oxygen has value in patients with acute CO poisoning. I therefore plan to refrain from further discussion in this context.

Sincerely,
Lindell Weaver, MD

REFERENCES

1. Scheinkestel CD, Bailey M, Myles PS, Jones K, Cooper DJ, Miller IL, Tuxen DV. Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: a randomised controlled clinical trial. *Med J Aust* 1999;170(5):203-10.
2. Weaver LK, Hopkins RO, Chan KJ, Churchill S, Elliott CG, Clemmer TP et al. Hyperbaric oxygen for acute carbon monoxide poisoning. *N Engl J Med* 2002; 347(14):1057-1067.
3. Weaver LK, Hopkins RO, Chan K, Thomas FO, Churchill SK, Elliott CG, Morris AH (invited). Carbon monoxide research group, LDS Hospital, Utah in reply to Scheinkestel et al. and Emerson: The role of hyperbaric oxygen in carbon monoxide poisoning. *Emerg Med Australasia* 2004; 16:394-9.

David Juurlink

Date received: September 18, 2006

Cite this comment as: <http://www.cochranefeedback.com/cf/cda/citation.do?id=9558#9558>

In response,

We regret that Dr. Weaver perceives our review as biased and our criticisms of his trial as hostile. The goal of our review was to inform clinical decision making, but we accept that our conclusions may not be shared by everyone.

Dr. Weaver presents several arguments that we will address in turn.

First, he contends that allocation concealment in his trial was adequate. Indeed, in our 2005 revision, we gave his study the highest possible rating ("A") on this characteristic (see Characteristics of Included Studies), making it the only study in the review with adequate allocation concealment. The passage he cites was a remnant from an earlier version of the review, and will be revised in the next substantive update. Despite Dr. Weaver's suggestions of bias on our part, we believe that our revision in 2005 of the allocation concealment grade for his study provides evidence to the contrary.

Second, he suggests we should not have included the findings of Scheinkestel et al.(1) in our analysis. Although it is customary to include published and unpublished information when preparing a systematic review, in response to Dr. Weaver's concern we have conducted a sensitivity analysis by excluding the study of Scheinkestel et al. The resulting analysis does not alter our conclusions regarding the efficacy of HBO for carbon monoxide poisoning (odds ratio for benefit 0.74, 95% confidence interval 0.48 to 1.14).

Third, Dr. Weaver states that his trial satisfied all of the criteria we deemed necessary for a definitive trial of hyperbaric oxygen for carbon monoxide poisoning. However, his trial was not a multicentre initiative, it did not employ an independent data safety monitoring committee, it did not stratify the analysis by relevant clinical sub-groups, and it was not registered prospectively. Although many proponents of HBO have characterized this trial as definitive, we respectfully disagree.

Fourth, Dr. Weaver maintains that his study evaluated 'meaningful outcomes.' This is an imprecise and highly subjective term. A fundamental principle of clinical trials is that the outcome of interest should be simple, objective and clinically relevant to individual patients. The outcome should not be derived, as Weaver's was, from complex interpretations of pooled differences in test scores, especially when those tests are not routinely conducted in clinical practice. Indeed, it is difficult to conceive how a meaningful outcome could label 46% of patients in the control group as having "cognitive sequelae" when in fact 5 of 6 of the mean test scores in that group were actually above average.

Finally, Dr. Weaver sidesteps our most important criticism of his study: the evolution, during the course of his trial, of the primary outcome from one destined to yield a negative outcome to one yielding a positive outcome. He ascribes this idiosyncrasy to errors in an editorial correspondence, but analysis of his writings suggests that this is not likely the sole explanation.

- Delayed Neurologic Sequelae (DNS) as the original primary outcome:

In 1995, Weaver and colleagues published the first interim analysis of their study.(2) In that report, the only test of statistical significance was applied to DNS, and the investigators indicated that enrolment would continue because the P value had not

achieved the threshold required for premature termination of the trial.

That same year, in the editorial correspondence he now contends was erroneous,(3) he presented a description of his ongoing trial and gave an explicit definition of its primary outcome, congruent with that described in the first interim analysis. He wrote:

“Our major question is, does HBO2 reduce the incidence of delayed neurologic sequelae (DNS)?”

He also wrote:

“During the course of the trial, it became evident that operational definitions of DNS and PNS were needed... Our definition for DNS is that (sic) development of a new neurologic abnormality not present at day 1, and/or decrement of neuropsychologic subtest score of more than 2 SD points below the mean or 2 subtest scores more than 1 SD point below the mean compared to standardized norms (prior normal neuropsychologic test). If the prior neuropsychologic test is abnormal, then we use a decrement of an abnormal subtest of more than 1 SD point compared to the prior score or more than 0.5 SD points below each of at least 2 abnormal subtests.”

Collectively, these writings confirm that DNS was the original intended outcome of their trial. This outcome has never been subsequently reported in any forum, and in neither the interim analysis nor his 1995 editorial correspondence was an analysis of “cognitive sequelae” conducted or even foreshadowed.

- “Cognitive Sequelae” as the eventual primary outcome:

By 2001, things had changed. In an editorial co-authored by Dr. Weaver,(4) a discussion of his soon-to-be published study contained no mention of DNS. Indeed, a very different outcome (“cognitive sequelae”) had been defined. He wrote:

“Cognitive sequelae were considered present if any 6-wk neuropsychological subtest score was >2 SD below the mean (or if at least two subtest scores were each more than 1 SD below the mean) of demographically corrected standardized scores. Cognitive sequelae were present if a neuropsychological subtest score was > 1 SD below the mean or if two subtest scores each were >0.5 SD below the mean and the patient complained of memory, attention, and/or concentration difficulties.” In the final publication,(5) the cut-off values used to define abnormal results changed yet again.

In summary, the original intended outcome of this trial was DNS defined by rigorous clinical criteria. In contrast, the final publication reports “cognitive sequelae,” a distinctly different outcome. We assert that a significant difference between HBO and NBO would almost certainly not have been demonstrated if the originally intended outcome had been analysed.

Dr. Weaver and his co-investigators have obviously collected the data necessary to examine DNS as an outcome, and we urge them to present this analysis. Doing so would help settle the present debate. While HBO enthusiasts may argue that ‘cognitive sequelae’ is a meaningful outcome, skeptics may legitimately wonder if the revised outcome was simply that which cast the most favourable light on HBO once all the data was collected.

Regrettably, the phenomenon of changing outcomes plagues clinical trials.(6-8) Chan and Altman found that compared to protocols, 62% of published trials presented at least one primary outcome that was changed, introduced, or omitted.(8) In fact, fully 86% of survey respondents initially denied the existence of unreported outcomes, despite clear evidence to the contrary from their earlier publications.(8) Chan and Altman concluded that published articles, as well as systematic reviews that blindly incorporate them, may therefore be unreliable and overestimate the benefits of an intervention.

David N. Juurlink BPhM, MD, PhD, FRCPC

Division Director, Clinical Pharmacology and Toxicology; Attending Physician, Division of General Internal Medicine; Scientist, Clinical Epidemiology Unit; all at Sunnybrook Health Sciences Centre, University of Toronto

Scientist, Institute for Clinical Evaluative Sciences

Medical Toxicologist, Ontario Regional Poison Information Centre

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(1) Scheinkestel CD, Bailey M, Myles PS, Jones K, Cooper DJ, Millar IL et al. Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: a randomised controlled clinical trial. *Med J Aust* 1999; 170(5):203-210.

(2) Weaver LK, Hopkins RO, Larson-Lohr V, Howe D, Haberstock D. Double blind, controlled, prospective, randomized clinical trial (RCT) in patients with acute carbon monoxide (CO) poisoning: outcome of patients treated with normobaric oxygen or hyperbaric oxygen (HBO) - an interim report. *Undersea & Hyperbaric Medicine* 1995;(22(suppl)):14.

(3) Weaver LK, Hopkins RO, Larson-Lohr V. Carbon monoxide poisoning: a review of human outcome studies comparing normobaric oxygen with hyperbaric oxygen. *Ann Emerg Med* 1995; 25(2):271-272.

(4) Hampson NB, Mathieu D, Piantadosi CA, Thom SR, Weaver LK. Carbon monoxide poisoning: interpretation of randomized clinical trials and unresolved treatment issues. *Undersea Hyperb Med* 2001; 28(3):157-164.

(5) Weaver LK, Hopkins RO, Chan KJ, Churchill S, Elliott CG, Clemmer TP et al. Hyperbaric oxygen for acute carbon monoxide poisoning. *N Engl J Med* 2002; 347(14):1057-1067.

(6) Chan AW, Altman DG. Identifying outcome reporting bias in randomised trials on PubMed: review of publications and survey of authors. *BMJ* 2005; 330(7494):753.

(7) Chan AW, Krljeza-Jeric K, Schmid I, Altman DG. Outcome reporting bias in randomized trials funded by the Canadian Institutes of Health Research. *CMAJ* 2004; 171(7):735-740.

(8) Chan AW, Hrobjartsson A, Haahr MT, Gotzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *JAMA* 2004; 291(20):2457-2465.

Lindell Weaver

Date received: July 3, 2006

Cite this comment as: <http://www.cochranefeedback.com/cf/cda/citation.do?id=9531#9531>

Dear editor:

The 2005 Cochrane Review on hyperbaric oxygen for carbon monoxide poisoning (unchanged in 2006) concluded there is "no evidence to support use of hyperbaric oxygen for treatment of patients with carbon monoxide poisoning" and called for a multi-center randomized controlled trial (1,2).

Only 2 of the six clinical trials included in their review enrolled all poisoned patients regardless of poisoning severity, Scheinkestel, et al., (3) and our study, published in the *New England Journal of Medicine (NEJM)* in 2002 (4). These 2 clinical trials were considered equivalent in the Cochrane analysis, yet these studies are not equivalent. In fact, according to the inclusion requirements for clinical trials in this review, it should not have even been included in the analysis. The Cochrane reviewers state, "Trials that used surrogate outcome measures, did not report a frequency of neurologic sequelae, or did not present data allowing the calculation of the frequency of neurologic symptoms at one month were excluded from the analysis" (1). Scheinkestel, et al. reported "sequelae at end of treatment" (at approximately 3-6 days following carbon monoxide poisoning) (3). Cochrane reviewers present two conflicting versions of unpublished one-month outcome data from the Scheinkestel, et al. trial (in Figure 1 and Table 1), but these data do not meet the Cochrane Review definition for inclusion. In addition, these data have not been available to the rest of the scientific community and lack peer-review. The review authors described these outcomes only as "symptomatic," which was not defined, and cognitive test scores were not shown.

The limitations of the study by Scheinkestel, et al. render it uninterpretable for clinical decision-making, and if the Cochrane Reviewers had followed their own rules, only one study that enrolled all poisoned patients, regardless of severity (4), would have been incorporated into the Cochrane review.

Despite harsh criticism by the Cochrane Review authors, our study satisfied all 22 items of the CONSORT Uniform Reporting Standards for randomized controlled trials (www.consort-statement.org) (5). In addition, our study satisfied the Cochrane Review authors' recommended criteria for a proposed multi-center randomized trial: triple-blind, sham "dives," meaningful outcomes, group sequential design, and data safety and monitoring board.

To summarize, we found a 6-week cognitive sequelae rate in 25% of subjects treated with hyperbaric oxygen therapy compared with 46% of patients treated with normobaric oxygen ($P=0.007$). When adjusted for cerebellar dysfunction and stratification, odds ratio = 0.45, $p = 0.03$; 95% CI = 0.129-0.919 (4).

The Cochrane Review authors make several criticisms our study that are ungrounded and hint at Cochrane Reviewer bias. For example, the authors state, "Allocation concealment was possibly adequate, but this could not be assured (graded B), and an element of selection bias cannot be excluded."

As defined in the Cochrane Review, allocation concealment categories are:

"A = trials deemed to have taken adequate measures to conceal allocation (i.e. centralized randomization; numbered or coded bottles or containers; serially numbered, opaque sealed envelopes, etc.);

B = trials in which the authors either did not report an allocation concealment approach at all, or reported an approach that did not fall into one of the other categories;"

However, the allocation concealment process for our study was described in the original publication as follows: "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; treatment-group assignments were given to respiratory therapists in protected, sequentially numbered, sealed, opaque envelopes" (4). The allocation concealment of this study clearly meets criteria for "A."

The Cochrane reviewers state, "Allocation concealment possibly jeopardized by fixed block size of 6." Allocation concealment in our study was not jeopardized. In fact, we took extraordinary efforts to maintain triple blinding, which was satisfied. Our research group was never contacted by the Cochrane reviewers to offer information regarding blinding and allocation concealment. I remain perplexed that our wording (4) misleads one to believe that allocation concealment was "possibly jeopardized." The statement that "selection bias cannot be excluded" is offered without evidence. The language concerning this issue in our article (4) speaks for itself.

The authors of this review allege, "Although the final publication describes a primary outcome of all neurologic sequelae, the originally intended endpoint was delayed neurologic sequelae," referencing a letter to the editor in 1995 (6). Our original prime outcome was 6-week cognitive sequelae, as defined in the *NEJM* paper (4). In our *NEJM* paper, we presented these 6-week cognitive outcomes, deeming it did not matter if outcomes were of the persistent or delayed variety.

In addition, the Cochrane reviewers state, "The definition of neurologic sequelae itself changes between the interim analysis ...and the final publication." This allegation is based upon a letter to the editor written in 1995 (6). Unfortunately the letter to the editor is inaccurate in its description of our definition of cognitive sequelae. Presumably, the Cochrane reviewers never considered that this 1995 letter might be inaccurate and less complete than what we published in the NEJM paper. Nevertheless, the definition we used in our NEJM paper (4) is correct and has been how we have defined cognitive sequelae from trial inception.

The review authors misunderstood our "group mean" data, stating, "the mean neuropsychological testing scores for patients treated with NBO were within the normal range." Table 3 in our NEJM article (4) shows neuropsychological subtest scores from all patients; those with cognitive sequelae are grouped with those patients without cognitive sequelae. Also, this point is addressed thoroughly in an article published in 2004 (7), not cited by the Cochrane Review. Despite the fact that this data was group mean, in which the patients with cognitive sequelae are obscured by those without cognitive sequelae, 3 of the 6 neuropsychological subtest scores approached significance $p=0.06$, 0.03 , 0.06 , respectively, favoring those patients treated with hyperbaric oxygen (To be ultra-conservative, we required a p-value less than 0.008 , using a Bonferroni correction (4), although this correction is deemed unnecessary by many neuropsychologists, since each neuropsychological subtest we used is independent of the others). Additionally, the point that "patients treated with NBO were within the normal range" is further explained by practice effects in patients without cognitive sequelae transiently raising their neuropsychological subtest scores.

The review authors are critical that "patients enrolled in the NBO arm of this appeared more ill than those in the HBO arm, with a longer mean exposure (22 hours vs. 13 hours) and a greater prevalence of cerebellar signs at baseline (15% vs. 4%). The degree to which this influenced outcomes is unknown." In fact, in Table 2 of our NEJM paper (4), we reported that in patients with normal cerebellar dysfunction, 6-week cognitive sequelae was 23.2% (HBO2) and 39.0% (NBO2), $p=0.05$. The carbon monoxide exposure duration was not statistically significant ($p=0.3$). The non-cited 2004 Emerg Med Australas article (7) also addressed these issues.

The Cochrane Review authors state "None [of these trials] reported significant long-term outcomes." Our NEJM article reported 12 month outcomes: "Cognitive sequelae at 6 months and 12 months were less frequent in the hyperbaric-oxygen group than in the normobaric-oxygen group, both according to the intention-to-treat analysis ($P=0.02$ at 6 months, $P=0.04$ at 12 months) and according to the efficacy analysis, ($P=0.03$ at 6 months, $P=0.08$ at 12 months)." This point is again discussed in Emerg Med Australas, 2004 (7).

The Cochrane Review authors have stated there is "no evidence to support use of hyperbaric oxygen for treatment of patients with carbon monoxide poisoning." Clearly, there is evidence to support the use of hyperbaric oxygen for treatment of patients with carbon monoxide poisoning.

Policy-making and patient care have been impacted by this Cochrane Review, and those are the worthy reasons to correct inaccuracies and point out obvious Cochrane Review author bias.

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peter PANG

Date received: March 8, 2003

Cite this comment as: <http://www.cochranefeedback.com/cf/cda/citation.do?id=9035#9035>

Weaver article is an landmark article.

I personally think that the study is flawed. But the comment by InfoPOEMs and Journal Watch are positive. Who is the judge?

I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Mike Bennett

Date received: October 14, 2002

Cite this comment as: <http://www.cochranefeedback.com/cf/cda/citation.do?id=8924#8924>

Just wanted to make sure the authors were aware of the full publication of the Weaver study in last week's New England Journal. I think it may contribute useful data to the meta-analysis and review.

Sorry, I don't have the full citation in front of me and will lose this window if I get out to get it!

Mike Bennett

I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.