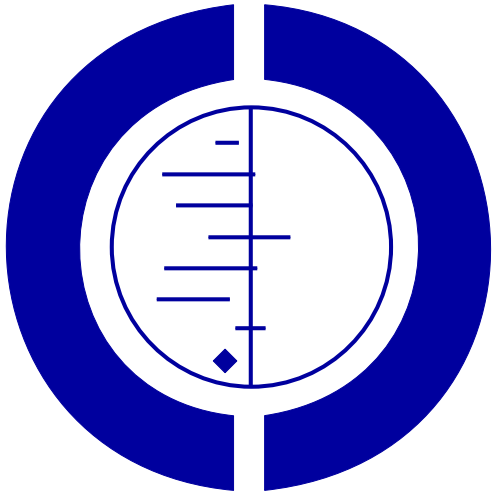
Hyperbaric oxygen for carbon monoxide poisoning (Review)

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



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ABSTRACT

Background
Poisoning with carbon monoxide (CO) remains an important cause of accidental and intentional injury worldwide. Several unblinded non-randomized trials have suggested that the use of hyperbaric oxygen (HBO) prevents the development of neurological sequelae. This has led to the widespread use of HBO in the management of patients with carbon monoxide poisoning.

Objectives
To examine randomized trials of the effectiveness of hyperbaric oxygen (HBO) compared to normobaric oxygen (NBO) for the prevention of neurologic sequelae in patients with acute carbon monoxide poisoning.

Search strategy
We searched MEDLINE (1966-present), EMBASE (1980-present), and the Controlled Trials Register of the Cochrane Collaboration, supplemented by a manual review of bibliographies of identified articles and discussion with recognized content experts.

Selection criteria
All randomized controlled trials involving non-pregnant adults acutely poisoned with carbon monoxide (regardless of severity), with adequate or unclear allocation concealment.

Data collection and analysis
Two reviewers independently extracted from each trial information on: the number of randomized patients, types of participants, the dose and duration of the intervention, and the prevalence of neurologic symptoms at follow-up.

Main results
Seven randomized controlled trials of varying quality were identified; one was excluded because it did not evaluate clinical outcomes. Of the six remaining trials, two represent incomplete publications (one interim analysis, one abstract). Of these six trials, four found no benefit of HBO for the reduction of neurologic sequelae, while two others did. Although pooled analysis does not suggest a benefit from HBOT (OR for neurological deficits 0.78, 95%CI 0.54 to 1.12, p=0.18), significant methodologic and statistical heterogeneity was apparent among the trials, and this result should be interpreted cautiously. Moreover, design or analysis flaws were evident in all trials. Importantly, the conclusions of one positive trial may have been influenced by failure to adjust for multiple hypothesis testing, while interpretation of the other positive trial is hampered by apparent changes in the primary outcome during the course of the trial.

Authors' conclusions
Existing randomized trials do not establish whether the administration of HBO to patients with carbon monoxide poisoning reduces the incidence of adverse neurologic outcomes. Additional research is needed to better define the role, if any, of HBO in the treatment of patients with carbon monoxide poisoning. This research question is ideally suited to a multi-center randomized controlled trial.

SYNOPSIS

No evidence to support use of hyperbaric oxygen for treatment of patients with carbon monoxide poisoning

Many people are poisoned by carbon monoxide gas, either intentionally (e.g. in suicide attempts) or by accident. Carbon monoxide interferes with oxygen transport in the body, and can also directly damage a variety of organs including the brain. The usual treatment involves removing the affected person from the source of the gas, general supportive care, and administering oxygen which hastens the elimination of carbon monoxide from the body. High pressure oxygen (hyperbaric oxygen) is only available at a few hospitals, and it is sometimes used to speed this process even further. However, the review of published trials found conflicting, potentially biased, and generally weak evidence regarding the efficacy of hyperbaric oxygen for the prevention of neurological symptoms.

BACKGROUND

Carbon monoxide (CO) is a colorless, odorless and tasteless gas generated during the incomplete combustion of carbon-based compounds. Poisoning with CO remains an important cause of accidental and intentional injury worldwide. In the United States alone, there are an estimated 1000−2000 accidental deaths due to carbon monoxide exposure each year, resulting from an estimated 40,000 annual exposures (Weaver 1999).

The pathophysiology of carbon monoxide exposure is incompletely understood. Upon exposure, CO binds to hemoglobin with an affinity 210 times than of oxygen, thereby decreasing the oxygen-carrying capacity of blood. In addition to generating carboxyhemoglobin, carbon monoxide has been shown to cause harm by several other mechanisms including direct disruption of cellular oxidative processes, binding to myoglobin and hepatic cytochromes, and peroxidation of brain lipids (Weaver 1999). Both effects lead to generalized hypoxia, varying degrees of end-organ damage, and occasionally death. The severity of poisoning is a function of the duration of exposure and the ambient concentration of CO, and the underlying health status of the exposed individual. Although useful for diagnosis when detected, the initial carboxyhemoglobin level correlates poorly with outcome (Seger 1994).

Two syndromes are recognized to occur after acute CO poisoning: persistent neurologic sequelae (PNS) and delayed neurologic sequelae (DNS) (Weaver 1999). The former is characterized by symptoms or signs referable to CO poisoning that may improve, although not to the premorbid state. The latter is characterized by a relapse of symptoms or signs referable to CO poisoning, occurring after a transient period of improvement. This deterioration may be abrupt and dramatic. In both instances, however, the symptoms are non-specific, and the entities may be difficult to distinguish from each other.

Standard treatment for CO poisoning includes removal from the site of exposure, administration of supplemental oxygen, and general supportive care. The elimination half-life of carboxyhemoglobin (approximately 320 minutes) is shortened approximately five-fold by the administration of 100% oxygen at atmospheric pressure (normobaric oxygen, NBO). The administration of 100% oxygen at pressures higher than atmospheric (hyperbaric oxygen, HBO) further hastens the elimination of carboxyhemoglobin (Jay 1997). Several unblinded, non-randomized trials and case series suggest that the use of HBO prevents the development of PNS and/or DNS. These observations have led some clinicians to use HBO for selected patients with carbon monoxide poisoning, although there is considerable variability in clinical practice.

Because HBO is available at only a few hospitals (necessitating the transfer of potentially unstable patients), is substantially more expensive than NBO, and is occasionally complicated by barotrauma and claustrophobia, its superiority over NBO in this setting should be established. This review was undertaken to examine the effect of HBO on the development of neurologic symptoms referable to CO poisoning one month after treatment.

OBJECTIVES

To examine the effectiveness of HBO in reducing the prevalence of neurologic symptoms approximately 4 to 6 weeks following treatment in patients with acute CO poisoning.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

The analysis was limited to randomized controlled trials, with or without blinding. 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.

Types of participants

All non-pregnant adults acutely poisoned by carbon monoxide.

Types of intervention

Studies were included in which patients with CO poisoning were randomized to receive either HBO or NBO.

Types of outcome measures

The main outcome measure of interest was the presence of persistent signs or symptoms possibly indicative of neurologic injury at follow-up (approximately 4 to 6 weeks) after randomization. No

universally accepted criteria exist for the diagnosis of persistent neurologic sequelae (PNS) or delayed neurologic sequelae (DNS) and outcomes were defined and measured differently in each study. In the absence of a well-defined, mutual outcome measure for all studies, we retained the definitions of neurologic sequelae presented by investigators in their reports. The symptoms were often non-specific and included headache, confusion, difficulty concentrating, and sleep disturbances, all of which are plausibly related to CO exposure.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: Injuries Group search strategy

Randomized controlled trials, without language restriction, were identified in a search of the MEDLINE database (1966 - present) and EMBASE, supplemented with manual searching of the reference lists of retrieved documents. A search of the Cochrane Central Register of Controlled Trials was performed with the assistance of a search strategist within the Injuries Review Group. Additional references were sought from experts who have published widely in the area.

The electronic search strategy was performed as follows:

Using OVID MEDLINE (1966-Oct 2004):

1. exp carbon monoxide/
2. exp CO/
3. monoxide.tw.
4. 1 or 2 or 3
5. exp hyperbaric oxygen/
6. hyperbaric.tw.
7. 4 and 6
8. clinical trial.pt.
9. 7 and 8

EMBASE (January 1980 - Sept 2004) was searched using the following strategy:

1. monox* (in ti, ab, kwds)
2. CO (in ti, ab, kwds)
3. or /1-2
4. hyperbar* (in ti, ab, kwds)
5. HBO (in ti, ab, kwds)
6. or /4-5
7. 3 and 6
8. controlled trial (in kmajor,kminor)
9. 7 and 8

An additional abstract not identified using the search strategies described above (Mathieu 1996) was identified in a manual search of the references of the other studies. Also identified were published abstracts of the interim analyses of three trials (Thom 1992; Scheinkestel 1996; Weaver 1995a).

The searches were last updated in October 2004.

METHODS OF THE REVIEW

All trials identified with this search strategy have been considered for inclusion in this review. Several trials of HBO with objectives other than treatment of carbon monoxide poisoning have been excluded without further evaluation. Two reviewers (DNJ, NAB) examined the electronic search results for trials that were possibly relevant, and these articles were retrieved in full.

The quality of each trial was independently assessed by three reviewers (DNJ, NAB, MBS) according to the method of Jadad (Jadad 1996). To be included in the primary analysis, a score of three or higher (out of a possible five) on this scale was required.

As there is evidence that the quality of allocation concealment affects the results of studies (Schulz 1995), both reviewers independently assessed the quality of each trial according to the method of Schulz (Schulz 1995) as shown below:

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

C = trials in which concealment was inadequate (such as alternation or reference to case record numbers or to dates of birth).

Where the method of allocation concealment was not reported, or where additional information was required to appropriately assess study quality, the principal authors of these trials were contacted for clarification. However, responses did not uniformly clarify these questions.

On occasion where the two reviewers disagreed on either the quality score or the adequacy of allocation concealment, agreement was reached through discussion in each instance. Two reviewers (DNJ, NAB) extracted data from each trial including information on the participants (age and gender distribution, mode of poisoning, carboxyhemoglobin level upon randomization, and history of loss of consciousness), the interventions (duration and dose of NBO and HBO), and presence of signs and symptoms at follow-up. Insufficient data were available to examine the effect of HBO in any subgroup of patients.

DESCRIPTION OF STUDIES

Seven potentially relevant trials were identified. One trial was excluded because of inadequate allocation concealment and the use of surrogate outcome measures (Ducasse 1995).

Of the remaining six trials, four are published in final form (Raphael 1989; Thom 1995; Scheinkestel 1999; Weaver 2002). One has been published as an interim analysis (Mathieu 1996) while another (Raphael 2004) is published in abstract form. Data from all six trials are incorporated in this review, although it is possible that more details regarding the latter two trials may become available when they are published in final form.

The patients, interventions, completeness of follow-up and outcomes assessment varied significantly among the trials (see section on included studies for full details). Only two trials (Scheinkestel 1999; Weaver 2002) employed 'sham dives', exposing control subjects to NBO in a hyperbaric chamber.

METHODOLOGICAL QUALITY

In each of the included studies, allocation concealment was possibly adequate but this could not be assured (graded B) and an element of selection bias cannot be excluded.

Applying the Jadad scale (Jadad 1996), one trial received a score of 2/5 (Mathieu 1996) and three trials received a score of 3/5 (Raphael 1989; Thom 1995; Raphael 2004); in each instance double-blinding was not possible as the control patients did not enter a hyperbaric chamber and the possibility of bias at several levels is particularly strong. Only two trials received scores of 5/5 (Weaver 2002; Scheinkestel 1999). These trials stipulated that outcome assessors were blind to treatment allocation.

Each study adequately outlined the numbers of patients lost to follow-up and reasons for this. Follow-up was poorest in the Scheinkestel study (Scheinkestel 1999), in which only 46% of subjects were evaluated one month after treatment.

RESULTS

The six trials enrolled a total of 1997 patients, of whom 1335 were randomized to either HBO or NBO and had outcomes recorded. The severity of CO poisoning, the treatment regimens, and outcome assessment varied significantly among trials.

The diagnosis of carbon monoxide poisoning was generally made by a history of exposure to carbon monoxide and an elevated carboxyhemoglobin level. The severity of CO poisoning varied in the individual trials. Two studies stratified randomization according to whether or not there was a history of loss of consciousness (Raphael 1989; Raphael 2004). In the earlier of these (Raphael 1989), only patients with no initial loss of consciousness were randomized to HBO, while in the latter (Raphael 2004), patients with transient loss of consciousness were randomized to HBO. In both of these studies, patients with more marked impairment of consciousness were randomized to different doses of HBO; these patients were not considered in this review. Two trials only enrolled patients with no loss of consciousness or cardiovascular instability (Thom 1995; Mathieu 1996), while two other trials included all patients with CO poisoning regardless of severity (Scheinkestel 1999; Weaver 2002).

Each principal investigator confirmed that virtually all patients received treatment with supplemental oxygen prior to randomization, which would be considered standard practice.

The duration, timing, and dose of both HBO and NBO varied greatly among studies. One study (Raphael 1989) used an active treatment of HBO at 2 atmospheres absolute (ATA) for two hours followed by 100% oxygen at atmospheric pressure for four hours, while the control group received 100% oxygen for six hours. Another trial (Thom 1995) varied the intensity of HBO in the active treatment arm, using 2.8 ATA for 0.5 hours followed by 2 ATA for 1.5 hours. In this trial the control group received 100% oxygen at 1 ATA for a variable duration (mean = 4.2 hours). A third trial, published thus far only as an interim analysis (Mathieu 1996), randomized patients to HBO at 2.5 ATA for 90 minutes or NBO for 12 hours.

The intervention in a fourth trial (Scheinkestel 1999) was unusual and substantially different from other studies. Patients randomized to active treatment received HBO at 2.8 ATA for 60 minutes followed by 100% oxygen by face mask for 40 minutes, but were then administered high-flow oxygen for the remainder of the day. This sequence was repeated daily for a total of three days. A further 28% received three additional treatments because they were deemed to have a poor outcome. The control group was treated with 100% oxygen for 100 minutes followed by high-flow oxygen, repeated daily for three days. Thereafter, 15% underwent the same three-day regimen repeated because they were felt to have a poor outcome.

In one recently published trial (Weaver 2002), patients in the active treatment arm received three sessions of HBO, including an initial treatment of 3 ATA for 1 hour followed by 2 ATA for 1 hour, with two additional 2-hour treatments of 2 ATA at 6-12 hour intervals. Controls underwent sham dives with NBO at 1 ATA. The remaining trial (Raphael 2004) included an active treatment arm of HBO at 2.0 ATA for 60 minutes followed by 4 hours of NBO, while controls were treated with 6 hours of NBO.

The prevalence of persistent signs or symptoms of CO poisoning (as defined by the investigators) at 4 to 6 weeks following treatment was 202 of 691 (29%) patients treated with HBO, compared with 219 of 644 (34%) patients treated with NBO. In a pooled analysis using a random effects model, no statistically significant reduction in neurologic sequelae was associated with HBO treatment (OR 0.78; 95% confidence interval 0.54 to 1.12), although the point estimate favored treatment. In light of the methodologic and statistical heterogeneity among the various trials, however, simple pooling of trial results is probably not appropriate.

Sub-group analyses of specific groups of patients (e.g. those with more severe poisoning, those with deliberate self-poisoning, or those who received treatment relatively early) was not possible because individual patient characteristics and outcomes could not be determined from each study.

Detailed review of the trials and, where available, earlier published abstracts of interim analyses, identified several aspects that warrant interpretive caution.

Raphael 1989
This trial found no benefit from HBO over NBO, but the investigators only permitted less severely poisoned patients to be randomized to HBO or NBO. Because interventions are, in general, most likely to show benefit in patients with more severe disease, the possibility of type II error in this trial cannot be excluded. Consequently, this trial does not disprove a benefit of HBO, particularly in more severely poisoned patients.

Thom 1995
This was the first published randomized trial to identify a benefit from the use of HBO. Outcome assessment in this trial was performed by unblinded clinicians. Review of an interim analysis published in 1992 raises the possibility that its positive findings resulted from failure to adjust for multiple comparisons. Specifically, the interim analysis described the outcome of 58 patients, and found no difference in symptoms for patients in the NBO vs. HBO arms (4 of 29 patients vs. 0 of 29 patients, respectively). Seven additional patients were recruited thereafter, three to the NBO arm (all of these patients experienced neurologic sequelae), and four to the HBO arm (none of these experienced neurologic sequelae). Although the recruitment of seven additional patients with this distribution of allocation and outcomes could be due to chance (p=0.014 by Fisher's exact test), it may reflect premature termination of the trial. A statistical penalty to adjust for inflation of the type I error rate was not introduced, and would have rendered the final result statistically insignificant.

Mathieu 1996
This trial is reported only as an interim analysis. Although no statistically significant difference in neurologic symptoms was found between treatment arms at 1 month (22% with HBO vs. 26% with NBO), a difference was reported at 3 months (15% vs. 9%; p=0.016). No significant difference was reported at 6 months follow-up (10% vs. 6% respectively; p= 0.09) or 1 year (5% vs. 4% respectively), although the final results of this trial have yet to be published. Of note, this trial is sometimes characterized as demonstrating a benefit to HBO (Thom 2002; Hampson 2004) based upon the findings at 3 months, despite a lack of adjustment for multiple hypothesis testing and the absence of a significant difference at other intervals.

Scheinkestel 1999
This is the only negative study published to date in which control patients received sham treatment in a hyperbaric chamber. The trial enrolled a relatively large number of patients with attempted suicide, and patients in both arms of the trial were treated with continuous normobaric oxygen for 3 days, which is not generally accepted as standard practice. The most serious threat to the interpretation of this study is that only 46% of patients randomized to treatment were followed up at 4 to 6 weeks. Because of the strong possibility that patients lost to follow-up were systematically different from those in whom follow-up testing was obtained, the results of this trial are difficult to interpret.

Weaver 2002
This is the only positive study published to date in which control patients received sham treatment in a hyperbaric chamber. While the design of this trial is generally superior to previously published ones and the effect size of HBO appears large, this trial's interpretation is hampered by three issues. First, although the final publication (Weaver 2002) describes a primary outcome of all neurologic sequelae, the originally intended endpoint was delayed neurologic sequelae (Weaver 1995). Second, the definition of neurologic sequelae itself changed between the interim analysis (Weaver 1995) which used different threshold scores for neurologic testing and did not rely on the presence of symptoms, and the final publication (Weaver 2002), in which non-specific symptoms were the primary determinant of a statistical difference between treatments. In the final publication (Weaver 2002), neuropsychological testing identified no difference between HBO and NBO; indeed, the mean neuropsychological testing scores for patients treated with NBO were within the normal range. Finally, 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%, respectively). The degree to which this influenced outcomes, in particular trail-making (which may be hampered by cerebellar dysfunction), is not known.

Raphael 2004
To date this trial has only been published in abstract form. Like the earlier trial by the same principal investigator (Raphael 1989), HBO and NBO were only compared in patients with less severe CO poisoning (most of whom returned to work by 1 month). As noted above, a type II error cannot be excluded, because more severely poisoned patients were randomized to different regimens of HBO.

DISCUSSION

This systematic review identified all published randomized controlled trials of HBO vs. NBO for the treatment of acute carbon monoxide poisoning. The six evaluable trials enrolled patients with carbon monoxide poisoning of varying severity, employed different regimens of hyperbaric and normobaric oxygen, had varying degrees of follow-up, and were subject to various biases and analytical flaws that may have substantially influenced their conclusions.

Only two of these trials (Scheinkestel 1999 and Weaver 2002) were conducted in a double-blind fashion, and none reported clinically significant long-term outcomes.

Although we present a pooled analysis of these six studies suggesting no statistically significant difference between HBO and NBO (OR 0.78; 95% confidence interval 0.54 to 1.12), we caution that the methodologic and statistical heterogeneity of the six trials renders this analysis difficult to interpret. Subanalyses by severity, intent, and duration of poisoning were not possible.

During the course of this review we also identified several publications authored by recognized content experts. These often promoted the use of HBO based on the results of the two positive trials (Thom 1995; Weaver 2002) and, occasionally, the 3-month analysis of Mathieu's study (Mathieu 1996; Thom 2002; Hampson 2004) without addressing the limitations set forth above.

AUTHORS' CONCLUSIONS

Implications for practice

Existing randomized controlled trials of HBO vs. NBO in the treatment of non-pregnant adults with acute carbon monoxide poisoning provide conflicting results regarding the effectiveness of HBO. All published studies have limitations that threaten and may invalidate their conclusions.

Based on the results of these trials, HBO cannot routinely recommended for the treatment of CO poisoning. It is possible that some patients, particularly those with more severe poisoning, may derive benefit from treatment, but this remains unproven.

Implications for research

Additional research is needed to further define the role, if any, of hyperbaric oxygen in the treatment of carbon monoxide poisoning in various subsets of patients. Because carbon monoxide poisoning is common, this research is ideally suited to a multi-center randomized trial.

In order to minimize bias, future studies should employ a triple-blind technique (investigators, patients, and outcome assessors) using sham dives in a hyperbaric chamber for control subjects. The use of meaningful clinical outcomes is encouraged, while multiple hypothesis testing and "multiple looks" at the data should be minimized unless investigators make appropriate statistical adjustments to minimize inflation of the type I error rate. Stratified analyses of several clinically important patient subgroups (including those with deliberate self-poisoning, impaired consciousness, and those treated shortly after exposure) should be conducted; these should also be planned ex ante.

Such a trial should be prospectively registered and monitored in an ongoing fashion by an independent data safety monitoring board.

Importantly, in the absence of conclusive evidence that patients with severe CO poisoning benefit from HBO therapy, exclusion of such patients from future trials is not justified. Indeed, the potential to demonstrate the effects of treatment is greatest in this population, because they are at the highest risk of adverse outcomes.

POTENTIAL CONFLICT OF INTEREST

None declared.

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Mathieu 1996
Methods	Prospective, randomized, unblinded trial. Allocation concealment unclear. Jadad score 2/5
Participants	575 non-comatose nonpregnant patients with no evidence of mixed poisoning.
Interventions	HBO at 2.5 ATA for 90 minutes (plus 15 minutes each for compression and decompression) vs. 12 hours of NBO.
Outcomes	Neuropsychologic testing at 1, 3, 6, and 12 months. 'Persistent neurological menifestations' were present in 23% of HBO arm and 26% of active treatment arm at 1 month, but detailed data not presented.
Notes	Interim analysis only. Recruitment complete but analysis not available at the time of this review.
Allocation concealment	B

Study	Raphael 1989
Methods	Prospective, randomized, unblinded trial. Randomization stratified according to history of loss of consciousness. Allocation by sealed opaque envelopes, not sequentially numbered. Only those with no history of LOC randomized to HBO vs. NBO; more severe patients randomized to different regimens of HBO. Jadad score 3/5.
Participants	629 adults admitted within 12 hours of termination of CO exposure. Inclusion: age > 15 y, admitted within 12 h, COHb > 10% (smoker) or 5% (nonsmoker) Exclusion: other intoxication, pregnancy, CV collapse, pulmonary edema, non-feasible HBO (technical problems etc.), difficulty in stratifying into groups A or B (by LOC), refusal by patient. Of enrolled patients, 343 were randomized to receive either HBO or NBO.
Interventions	Only those without history of loss of consciousness randomized to HBO vs. NBO. A0 - 100% oxygen x 6h - other patients randomized to HBO x 1 vs. HBO x 2; not included in analysis. A1 - HBO x 2h followed by 100% oxygen x 4h (where HBO regimen included 30 mins compression & decompression flanking 60 mins at 2.0 ATA.)
Outcomes	Intention to treat analysis. Outcome measures included self-assessment questionnaire and physical examination by neurologist (unblinded) at one month, with no difference in outcome (symptoms present in 50 of 158 patients (32%) treated with NBO vs. 51 of 159 patients (32%) treated with HBO at one month.)
Notes	
Allocation concealment	B

Study	Raphael 2004
Methods	Prospective, randomized, unblinded trial. As with earlier trial by the same investigators, randomization was stratified by history of transient loss of consciousness vs. coma. Patients without impaired consciousness were excluded. Only patients with transient loss of consciousness were randomized to HBO vs NBO, albeit by an unclear method. Jadad score 3/5.
Participants	Patients with moderate to severe uninentional CO poisoning. Detailed inclusion and exclusion criteria were not specified.
Interventions	Patients in active treatment arm received HBO at 2.0 ATA for 1 hour followed by NBO for 4 hours, while control patients received NBO for 6 hours.
Outcomes	Outcome measures included self-assessment questionnaire and examination by a blinded neurologist at 1 month. No difference in primary outcomes was evident, with symptoms present in 29 of 74 patients (39%) randomized to NBO vs. 33 of 79 patients (42%) randomized to HBO.

Characteristics of included studies (*Continued*)

Notes	Presented in abstract form only (not an interim analysis).
Allocation concealment	B

Study	**Scheinkestel 1999**
Methods	Prospective double-blind RCT of HBO vs. NBO. Cluster randomization for patients presenting simultaneously. Allocation through sealed opaque envelopes, not sequentially numbered. Patients and outcome assessor blind to allocation, technicians and nurses not. Stratified by vent/non-vent and suicide vs. accidental exposure. Jadad score 5/5.
Participants	230 patients sequentially referred to single center in Australia. Inclusion: all referred. Excluded (n=39): children, burn victims, pregnant. Two groups similar for all important variables. 89% male, coma in 50.6%, average COHb 21%. Large number of suicide attempts (69%), co-intoxication (44%), and severe poisonings (73%).
Interventions	All patients given high-flow O2 prior to randomization. Daily treatment (x3) of HBO (100 minutes; 60 minutes at 2.8 ATA) OR NBO (100 minutes of 100% O2 at 1 ATA) as a sham dive. After third treatment, patients with deficits were treated again, with high-flow oxygen in between. 3 additional courses of original therapy given to 28% HBO and 15% NBO because of "poor outcome".
Outcomes	191 randomized (104 HBO NBO 87, discrepancy due to cluster) No mortality difference at discharge. Poor follow-up attendance (46%) at one month. 34/52 symptomatic in HBO arm vs. 20/34 symptomatic in NBO arm (NS).
Notes	Several other conclusions in text, based upon repeated neuropsychologic testing. However, no adjustment for multiple comparisons; high likelihood of spurious statistical significance.
Allocation concealment	B

Study	**Thom 1995**
Methods	Prospective, randomized, unblinded trial of HBO vs. NBO. Treatment allocation by computer-generated random numbers within sealed opaque envelopes, not sequentially numbered. Jadad score 3/5
Participants	65 patients referred from local emergency departments, within 6 hours of removal from exposure. Inclusion criteria: history of acute exposure, elevated COHb, symptoms consistent with CO poisoning. Exclusion criteria: history of LOC, active ischemia. Two groups largely similar (higher average COHb in HBO group 24.6% vs. 20.0%)
Interventions	All patients in HBO arm given 100% O2 until HBO initiated. HBO begun within 6 h of end of exposure. HBO @ 2.8 ATA for 30 minutes, then 2.0 ATA x 90 minutes. NBO 100% O2 until all symptoms resolved (mean 4.2 +/- 0.3 h). After intervention, neuropsychologic baseline testing (6 tests) performed (some up to 12 hrs. post-Rx). Occurrence of DNS self-reported as (1) recurrent symptoms or (2) new symptom consistent with DNS, plus deterioration in 1 or more subtest upon retesting.
Outcomes	Outcome assessors not blind to treatment allocation. 5 patients lost to follow up (2 control, 3 HBO). 7/30 patients in control arm had sequelae consistent with DNS vs. 0/30 patients in HBO arm.
Notes	No statistical adjustment for multiple comparisons (previous analysis published as abstract in 1992) raising concerns of spurious false positive results, particularly in light of recruitment and outcome pattern of the final seven patients recruited to trial.
Allocation concealment	B

Study	**Weaver 2002**
Methods	Prospective, randomized, double-blind RCT of HBO vs. NBO. Randomization method used sequentially numbers sealed envelopes. Jadad score 5/5. Allocation concealment possibly jeopardized by fixed block size of 6.

Characteristics of included studies (*Continued*)

Participants	152 patients with CO poisoning (symptomatic and COHb > 10% or symptoms and signs unequivocally due to CO exposure). Exclusions: Pregnancy, > 24h since exposure, < 16 years of age, moribund, refused consent. Stratified by LOC, age < 40, and delay to treatment < 6h.
Interventions	HBO - 1 session 3ATA x 1h & 2ATA x 1h, followed by two sessions 2ATA x 2h at 6-12 hour intervals. NBO patients received sham treatment at 1 ATM. Oxygen not routinely used after first session.
Outcomes	Serial neuropsychological testing immediately after treatments 1 and 3, and then at 2, 6, 26 and 52 weeks follow-up.
Notes	Endpoint in published trial different from that described in initial report of first interim analysis and earlier published descriptions of trial.
Allocation concealment	A

Characteristics of excluded studies

Ducasse 1995	Surrogate outcomes (EEG, cerebral blood flow reactivity to acetazolamide) examined rather than symptoms of DNS.

GRAPHS

Comparison 01. Hyperbaric Oxygen (HBO) vs. Normobaric Oxygen (NBO)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Presence of symptoms or signs at time of primary analysis (4-6 weeks)	6	1335	Odds Ratio (Random) 95% CI	0.78 [0.54, 1.12]

INDEX TERMS

Medical Subject Headings (MeSH)

Carbon Monoxide Poisoning [therapy]; Hyperbaric Oxygenation; Oxygen Inhalation Therapy; Randomized Controlled Trials

Medical MeSH check words

Humans

COVER SHEET

Title	Hyperbaric oxygen for carbon monoxide poisoning
Authors	Juurlink DN, Buckley NA, Stanbrook MB, Isbister GK, Bennett M, McGuigan MA
Contribution of author(s)	DJ screened citations for eligibility, obtained references, contacted authors, extracted data, entered data and wrote the review. NB, MS, and MB screened citations for eligibility, extracted data and helped to write the review. GI and MM obtained references and helped to write the review.
Issue protocol first published	2000/2
Review first published	2000/2
Date of most recent amendment	19 November 2004
Date of most recent SUBSTANTIVE amendment	03 November 2004

What's New	The search was updated in October 2004. Two new trials have been added (Weaver 2002, Raphael 2004), although the latter is published only in abstract form. The discussion section has been revised accordingly, and now includes a critical overview of some of the methodologic and statistical limitations presented by each of the published trials.
Date new studies sought but none found	03 June 2003
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	03 November 2004
Date authors' conclusions section amended	Information not supplied by author
Contact address	Dr David Juurlink Institute for Clinical Evaluative Sciences G-106 Sunnybrook and Women's College Health Sciences centre 2075 Bayview Avenue Toronto Ontario M4N 3M5 CANADA E-mail: david.juurlink@ices.on.ca Tel: +1 416 480 6100 Fax: +1 416 480 6048
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GRAPHS AND OTHER TABLES

Fig. 1. Comparison 01. Hyperbaric Oxygen (HBO) vs. Normobaric Oxygen (NBO)

01.01 Presence of symptoms or signs at time of primary analysis (4-6 weeks)

Review: Hyperbaric oxygen for carbon monoxide poisoning

Comparison: 01 Hyperbaric Oxygen (HBO) vs. Normobaric Oxygen (NBO)

Outcome: 01 Presence of symptoms or signs at time of primary analysis (4-6 weeks)