WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care

Worksheet author(s)

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January 31, 2010

Clinical question.

ALS-SC-073-05A:

Primary Clinical Question:
In adults with cardiac arrest (prehospital or in-hospital) due to carbon monoxide toxicity (P), does use of any disease-specific therapy (I) as opposed to standard care (C), improve outcome (O)?

Secondary Clinical Question:
In adults with severe cardiovascular toxicity or life-threatening toxicity (prehospital or in-hospital) due to carbon monoxide toxicity (P), does use of any disease-specific therapy (I) as opposed to standard care (C), improve outcome (O)?

The only disease-specific therapy studied with human outcomes is hyperbaric oxygen therapy.

Is this question addressing an intervention/therapy, prognosis or diagnosis? Intervention

State if this is a proposed new topic or revision of existing worksheet: New topic

Conflict of interest specific to this question

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No (see below)


Search strategy (including electronic databases searched).

Because hyperbaric oxygen therapy is the only specific therapy approved, generally recommended, or frequently considered for the immediate management of acute severe carbon monoxide poisoning, our main search was limited to this modality:

Ovid MEDLINE: Carbon Monoxide Poisoning (MeSH) AND Hyperbaric Oxygenation (MeSH); LIMIT humans

EMBASE: [‘Carbon monoxide poisoning’exp OR ‘Carbon monoxide poisoning’ (keyword)] AND [‘Hyperbaric oxygen’exp OR ‘hyperbaric oxygen’ (keyword)]; LIMIT human

Cochrane CENTRAL and DARE: “Carbon monoxide poisoning” (keyword) AND “Hyperbaric oxygen” (keyword)

ECC EndNote X Master Library: “Carbon monoxide” (keyword) AND “hyperbaric” (keyword) AND “clinical trial” (keyword).

After removal of duplicates, this search strategy produced 1,266 apparently unique references. These references were hand-searched for inclusion and exclusion criteria.

In order to test the assumption that hyperbaric oxygen therapy was the only modality with significant human data, we ran two additional searches (MEDLINE database, Ovid search engine, January 22, 2010):
Carbon monoxide poisoning (MeSH) / dt (drug therapy) LIMIT humans: 43 citations; 0 met inclusion criteria
Carbon monoxide poisoning (MeSH) / th (therapy) LIMIT humans: 757 citations; Although the studies cited below were also identified by this search strategy, 0 additional studies were identified that met inclusion criteria.

- State inclusion and exclusion criteria

Inclusion criteria:
(1) Human prospective randomized clinical trials comparing hyperbaric oxygen therapy with standard therapy (oxygen delivered via mask or endotracheal tube at ambient pressure).
(2) Human consecutive patient case series’ containing specific data about patients treated with any modality for carbon monoxide poisoning that produced cardiac arrest or severe cardiovascular toxicity (myocardial infarction, hypotension, or life-threatening dysrhythmia).

Exclusion criteria:
(1) Non-human studies
(2) Review articles
(3) Articles published in abstract form only
(3) Single patient case report and convenience sample case series
Number of articles/sources meeting criteria for further review:

Seven treatment studies met criteria for further review (Ducasse, 1995, 9; Thom, 1995, 474; Mathieu, 1996, xx; Raphael, 1999, 414; Scheinkestel, 1999, 203; Weaver, 2002, 1057; Raphael 2004, 455). Raphael, 2004, 455 and Mathieu, 1996, 7 were excluded because they have been published in abstract form only. The remaining 5 studies were graded and placed on the evidence table.

In addition, three consecutive patient case series’ were identified that included patient with cardiac arrest. Hampson, 2001, 36 is a report of 18 consecutive patients with ROSC following cardiac arrest due to carbon monoxide poisoning who received hyperbaric oxygen treatment. A subsequent case series (Hampson, 2008, 2523) includes 1,505 consecutive patients with CO poisoning of all severities, including this cohort. Two additional consecutive patient case series (Sloan, 1989, 629; Chou, 2000, 151) include sufficient data to identify outcomes in patients following ROSC from CO-associated cardiac arrest, and are therefore included. All patients in these series received hyperbaric oxygen therapy. One consecutive patient case series of CO poisoned patients treated without hyperbaric oxygen was identified (Meert, 1998, 149). Although this report describes the number of patients who survived the event, the number who had neurologically intact survival, and the number with various manifestations of severe cardiovascular toxicity (hypotension, etc.), it does not provide sufficient detail to calculate survival and/or neurologically intact survival rates for any subgroup. It was therefore excluded.

One additional case series (Goulon, 1986, 23) contains specific information about patients with severe cardiovascular toxicity.
Summary of evidence

Evidence Supporting Primary Clinical Question

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Level of evidence

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  
Italics = Animal studies

No articles were found to support the primary clinical question

Evidence Supporting Secondary Clinical Question

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### Evidence Neutral to Primary Clinical question

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It is impractical to apply hyperbaric oxygen therapy to patients during a period of cardiac arrest.

Three consecutive-patient case series (all LOE 4, good to fair quality) describe cohorts of patients who suffered cardiac arrest in the setting of carbon monoxide (CO) poisoning, developed ROSC, and were treated with hyperbaric oxygen (HBO). Survival to hospital discharge was universally poor: 0/18 (0%) (Hampson, 2001, 36), 6/23 (26%) (Sloan, 1989, 629), and 4/12 (25%) (Chou, 2000, 51). None of these studies reported neurologically intact survival in the cardiac arrest group. Clearly, the prognosis for survival to hospital discharge following CO-associated cardiac arrest, even among those achieving ROSC, is low; hyperbaric oxygen therapy is unlikely to benefit, or harm, these patients. A comparison cohort of CO-poisoned patients who did not receive hyperbaric oxygen following ROSC could not be identified. Therefore, the above results cannot be used to support statements about the benefit or harm from HBO.

A large consecutive-patient case series of hyperbaric-treated patients (Hampson, 2008, 2523 – LOE 4, good quality) evaluated factors predictive of 90-day mortality in 1435 CO poisoning survivors and 38 non-survivors (including the 18 non-survivors reported in Hampson, 2001, 36). Stepwise logistic regression analysis found that severity of acidosis and intubation during hyperbaric oxygen therapy were independent predictors of mortality. Like the Hampson, 2001, 36 study, this is a prognostic study which cannot be used to compare the effectiveness of therapies. Given the low overall mortality rate (2.6% in Hampson, 2008, 2523, and 3.9% in eight previously published studies summarized in the discussion), it is unlikely that an adequately-powered study on the effect of hyperbaric oxygen therapy on CO poisoning mortality can ever be conducted.

Goulon, 1986, 23 (LOE 4, poor quality) reported on 302 patients with CO poisoning, including 87 patients with hypotension (systolic BP < 80 mmHg, termed “circulatory failure” in this manuscript. In addition to IV fluids and isoproteranol, 73/87 patients with hypotension received HBO. 77/87 patients with hypotension survived to hospital discharge. The relationship between treatment with HBO and survival was not reported, which greatly limits the ability to draw conclusions from this manuscript.

The majority of the literature concerns the ability of hyperbaric oxygen to mitigate neurological injury after serious carbon monoxide poisoning. Well-conducted animal studies exist both to support (e.g. Thom, 1990, 340) and refute (Gilmer, 2002, 1) the ability of HBO to improve neurological outcomes, though the preponderance of animal evidence suggests benefit. Because several randomized human clinical trials were available to directly address this subject, we excluded animal studies, uncontrolled human case series, and case reports from this review.

The human randomized clinical trials provide no data about overall survival, and show mixed results on the question of neurologically intact survival. A well-written systematic review (Buckley, 2005, 75) and an equally well-written metaanalysis (Juurlink, 2005, CD002041) conclude that the data about whether hyperbaric oxygen therapy improves neurologically intact survival following carbon monoxide poisoning are inconclusive. Although these reviews are both LOE 1, it is important to note that few of the patients in the included studies suffered cardiac arrest or severe/life-threatening acute cardiovascular toxicity at the time of poisoning.

Only two human clinical trials enrolled patients with severe cardiovascular toxicity. Scheinkestel, 1999, 203 (LOE 1, fair quality) enrolled patients of all severity. Of 191 patients enrolled in this trial, 5 had hypotension and 1 had cardiac arrest. This study found no difference in neurological outcomes at hospital discharge or at 1-month follow-up. Six patients died in this study, equally distributed between the HBO and normobaric oxygen groups. The power of this study to detect differences in the most clinically meaningful (30-day) endpoint were limited by a 54% lost-to-follow-up rate, which resulted in its designation as fair quality). Survival and neurologically intact survival were not reported separately for the subgroup with severe cardiovascular toxicity.

Weaver, 2002, 1057 (LOE 1, fair quality) was well-designed and well-executed, but concerns have been raised about post hoc changes in the primary outcome of the study (see Juurlink, 2005, CD002041 and Buckley, 2005, 75 for a discussion of these issues, which resulted in its designation as fair quality). In this study population, 8% of patients were intubated; the proportion with cardiac arrest or hypotension is not reported. This study found a strong treatment effect in which treatment with HBO was associated with a significant increase in neurologically intact survival (75% with HBO vs. 46% with standard therapy).

The other trials excluded patients with severe cardiovascular toxicity, and are therefore LOE 5 for this clinical question. Patients with altered mental status or a history of loss of consciousness were also excluded from randomization to normobaric oxygen in these studies. Of these, one report (Thom, 1995, 474; LOE 5, poor quality) showed an improvement in neurologically intact survival with HBO. One report (Ducasse, 1995, 9; LOE 5, poor quality) used a surrogate outcome marker (cerebral blood flow reactivity to acetazolamide challenge) that had not been shown to correlate with patient-oriented outcomes of neurological function, and
therefore was rated neutral to the clinical question. One trial (Raphael, 1989, 414; LOE 5, poor quality) found no difference in neurological outcome.

Although it did not specifically report outcomes for patients with severe cardiovascular toxicity, one prognostic study (LOE 4, good quality) (reported as Satran, 2005, 1513 and Henry, 2006, 398) showed that CO poisoning victims treated with HBO who developed myocardial injury had increased cardiac and all-cause mortality, compared to those with normal cardiac injury biomarkers through a median of 7.6 years of follow-up. Because of its design, this study cannot be used to support statements about immediate treatment (including hyperbaric oxygen therapy), diagnostic testing, or late interventions that might mitigate this effect.

Acknowledgements:

Citation List

References included in the evidence table:

Buckley, 2005, 75

In this evidence-based medicine review, Buckley, Juurlink, and colleagues found no evidence that hyperbaric oxygen therapy improves neurologically intact survival following carbon monoxide poisoning. Although this systematic review is LOE 1 and of excellent methodologic quality, it is unclear how many of the subjects in the included trials had severe cardiovascular toxicity at the time of poisoning.

Chou, 2000, 151

Level 4. Neutral to the primary question

This prognostic study examined the effect of, smoke inhalation, and various clinical features on the risk of death following CO poisoning. Although cardiac arrest was a stronger prediction of death than any other factor analyzed in this series, some patients did survive after reported CO-associated cardiac arrest. Details about the cardiac arrest presentations, the exact proportion of cardiac arrest victims who survived, and their functional outcomes are not reported.

Ducasse, 1995, 9

Level 5. Neutral to the secondary question.

This study was determined to be neutral to the secondary question because no clinical outcome data were presented.

Hampson, 2001, 36

Level 4. Opposed to the primary question.

Because the outcome of interest was survival to hospital discharge, the retrospective design of this consecutive patient case series is a minor weakness. Despite receiving hyperbaric oxygen therapy, no patient (0/18) in this series survived to hospital discharge. However, rare case reports documenting survival do exist.

Juurlink, 2005, CD002041
In this Cochrane Collaboration review, Juurlink, Buckley, and colleagues found no evidence of benefit from hyperbaric oxygen therapy. Although this is a LOE 1 meta-analysis, it is unclear how many of the patients in this body of literature had acute, life-threatening cardiovascular toxicity from CO poisoning.

**Raphael, 1989, 414**  
Level 5. Opposed to the secondary clinical question.

This was a large, though somewhat methodologically weak, clinical trial. Patients with mild CO poisoning (no loss of consciousness, altered mental status, or hypotension) were randomized to receive one HBO treatment session, or standard care. Neurologically intact survival was the same in both treatment arms. Patients with more severe CO poisoning were randomized to receive one vs. two HBO treatment sessions. Neurologically intact survival was again the same in both treatment arms.

**Satran, 2005, 1513, and Henry, 2006, 398**  

These two publications report related outcomes from the same consecutive patient case series of patients referred for hyperbaric oxygen therapy. Severe carbon monoxide poisoning is associated with cardiac injury, which is, in turn, associated with an increase in short- and long-term all-cause mortality. This study provides no information about whether patients would have fared worse, the same, or better without hyperbaric oxygen therapy.

**Scheinkestel 1999, 203**  
Level 1. Neutral to the secondary clinical question.

Although the authors’ conclusion suggested a harm from hyperbaric oxygen therapy, these appear to be multiple, post-hoc comparisons made at a clinically unimportant time point (at the conclusion of hospitalization, 3-6 days after poisoning). No difference in any outcome was observed when patients were assessed the more clinically relevant time point, 30 days after poisoning. Although this may have been due to loss of statistical power (54% of patients were lost to follow-up at 30 days), I believe this study is best regarded as showing neither benefit nor harm from hyperbaric oxygen therapy.

**Sloan, 1989, 629**  
Level 4. Neutral to the primary question

In this case series of patients who received HBO, 23 patients were reported to have had cardiac arrest before and/or during HBO2 therapy. However, the total number of deaths in this series is 17 patients. Therefore, some patients survived after reported cardiac arrest. Details about the cardiac arrest presentations, the exact proportion of cardiac arrest victims who survived, and their functional outcomes are not reported.

**Thom, 1995, 474**  
Level 5. Favorable to the secondary question.

This prospective clinical trial randomized patients with mild to moderate carbon monoxide poisoning to hyperbaric vs. typical oxygen therapy delivered at ambient pressure. Patients with loss of consciousness, chest pain, and ischemic changes on electrocardiogram were excluded. The results were strongly favorable to hyperbaric oxygen therapy. Although all patients were neurologically normal immediately after treatment, 23% of patients (7/30) in the ambient pressure oxygen group, compared with
0% of patients (0/30) in the hyperbaric oxygen group, subsequently developed neurological complaints accompanied by abnormal neurocognitive testing.

Weaver, 2002, 1057

This well-designed, well-conducted study prospectively enrolled patients of all degree of clinical severity; half of study subjects had lost consciousness, and 8% were intubated at the time of the first treatment. The results were strongly favorable to hyperbaric oxygen therapy; in the intention-to-treat analysis, cognitive sequelae six weeks after poisoning, were observed in 46% of control and 25% of hyperbaric-treated patients. This study has been criticized by several authors, including Buckley, 2005, 75 (cited below), who raise concerns that the primary endpoint reported in this study was described by Weaver and colleagues in several earlier publications as a secondary outcome.

References not included in the evidence table:

Gilmer, 2002, 1

In contrast to Thom’s findings, hyperbaric oxygen therapy did not prevent neurological injury from carbon monoxide poisoning in Gilmer’s model. This may be because Gilmer’s model, but not Thom’s, induces central apnea and tissue hypoxia.

Hampson, 2008, 2523

This well-written retrospective case series provides useful data about prognostic factors correlated with fatal outcomes following CO poisoning. It does not provide data that directly address the clinical question of whether treatment with HBO should be administered or withheld from any particular patient group.

Mathieu, 1996, 7

Abstract publication only.

Unfortunately, this prospective clinical trial was never published in manuscript form; further information about the methods and results are not available.

Raphael, 2004, 455

Abstract publication only.

Only the group A patients in this series were randomized to HBO2 vs. standard oxygen therapy. Outcomes were the same in both treatment groups. This study was not blinded, and outcome measures were subjective. The 2004 report is an abstract presentation of 179 additional group A patients; methods and outcomes were essentially identical.

Thom, 1990, 340

This is the first of many well-conducted rodent studies in Thom’s lab in which hyperbaric oxygen therapy completely ameliorates the neurological injury caused by carbon monoxide poisoning.