CARBON MONOXIDE POISONING

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Rationale

The injuries caused by carbon monoxide (CO) traditionally have been viewed as due to a hypoxic stress mediated by an elevated carboxyhemoglobin (COHb) level. While hypoxic stress is clearly an element of poisoning, some injuries appear to be mediated by systemic oxidative stress. Perivascular and neuronal injuries arise by mechanisms other than hypoxia.[1,2] Neuropathology is due to a complex cascade of biochemical events involving several pathophysiologic processes,[3-10] some independent of pure hypoxic stress[11-13]. Furthermore, the COHb level does not correlate with the development of neurological or cognitive sequelae.[14-18]

The two organ systems most susceptible to injury from CO are the cardiovascular and central nervous systems. Human and animal data indicate that major cardiac injury at the time of poisoning is due primarily to CO-induced hypoxic stress.[19-21] In addition, the risk for cardiovascular-related death in patients with initial CO-induced cardiac injury appears to be increased over the 10 years following injury.[22] Many neurological problems can follow CO poisoning and include motor weakness, peripheral neuropathies, hearing loss, and Parkinsonian-like syndrome. Cognitive sequelae following CO poisoning are common. Also, the incidence of anxiety and depression is high following acute CO poisoning and may not be influenced by hyperbaric oxygen therapy (HBO_2).[23]

Administration of supplemental oxygen is the cornerstone of treatment of CO poisoning, although there are no clinical trials demonstrating improved outcomes using oxygen therapy administered at atmospheric pressure. Nevertheless, supplemental oxygen inhalation will hasten dissociation of CO from hemoglobin and provide enhanced tissue oxygenation. HBO_2 hastens COHb dissociation compared to breathing pure oxygen at sea-level pressure.[24-27] Additionally, HBO_2, but not ambient pressure oxygen treatment, has several actions, which have been demonstrated in animal models to be beneficial in ameliorating central nervous system (CNS) injuries. These include an improvement in mitochondrial oxidative processes,[28,29] inhibition of lipid peroxidation,[30] and impairment of leukocyte adhesion to injured microvasculature.[31] Animals poisoned with CO and treated with HBO_2 have been found to have more rapid improvement in cardiovascular status,[24] lower mortality,[32] and lower incidence of neurological sequelae.[33,34]

Since 1960, the clinical use of HBO_2 for CO poisoning has occurred with increasing frequency. Over 1,500 CO-intoxicated patients were treated in North American hyperbaric chambers from 1992 – 2002.[35] However, this number represents only a small fraction of those poisoned with CO. Extrapolation of data from a 1994 survey across three western states[36] and from Utah for 1996 and 1997,[37] gives an estimate that over 40,000 CO-poisoned patients are evaluated in emergency departments annually in the United States. Among patients treated with HBO_2, both mortality and neurocognitive morbidity are improved beyond that expected with ambient pressure supplemental oxygen therapy.[38-43] The optimal benefit from HBO_2 occurs in those treated with the least delay after exposure.[39] In selected patients, repeated treatments may yield a better outcome than a single treatment.[43]

Randomized trials

There are five published randomized clinical trials in acute CO poisoning, with conflicting results.[44-48] In the study by Raphael et al, no statistically significant benefit was observed when HBO_2 at 2 atmospheres absolute (atm abs) was compared with normobaric oxygen therapy.[44] However, the lack of benefit with HBO_2 may be attributed to nearly half of the study group being treated more than 6 hours after exposure and with an insufficient dose of HBO_2.[49] Conclusions from this study are further compromised by the lack of neuropsychological outcome measures and because only mildly poisoned patients were used in the comparative trial (no patients had loss of consciousness).

In terms of the mechanisms proposed for HBO_2 in CO poisoning, lower treatment pressures may have less impact on recovery of mitochondrial metabolism.[29] A partial pressure of oxygen greater than 2.0 atm abs is necessary to achieve maximum inhibition of adhesion molecules in human polymorphonuclear leukocytes.[50] The latter mechanism is an important HBO_2-related beneficial property modulating CO-mediated oxidative injury.[31]

The studies by Ducasse, et al. and Thom, et al. were both prospective, randomized clinical trials involving treatment at 2.5-2.8 atm abs within 6 hours of poisoning, and both studies found significantly better outcomes with hyperbaric vs. normobaric pressure oxygen treatment.[45,46] The lack of blinding potentially limits the strength of inferences one can draw from these two studies.

A blinded randomized clinical trial from Australia demonstrated that HBO_2 therapy did not improve outcome at hospital discharge (approximately 3 days after poisoning) as compared to 3 to 6 days of in-patient high flow mask (or endotracheal tube) O_2.[47] This trial has several important methodological issues that limit confidence in the conclusions, including: 1) One month cognitive outcomes were not reported. Rather only cognitive outcomes after a few days after poisoning were reported. 2) Poor 1-month follow-up; only 46% of enrolled patient returned for 1-month evaluation. 3) Patients in the control group were treated unconventionally, receiving 3 to 6 days of high concentrations of supplemental normobaric O_2. 4) Cluster randomization was employed which might have biased the results. 5) No intention-to-treat analysis was performed, although with a low follow-up rate the results probably would be similar. 6) The neuropsychological testing instrument could not discern depression from cognitive dysfunction.[51] Over half the patients had attempted suicide, raising a major question about the true incidence of neurological sequelae in this trial.

A recent double-blind randomized clinical trial with high follow-up rates, with analysis by intention-to-treat and with all enrolled patients accounted for in the results, demonstrated an impressive reduction in 6-week neuropsychological sequelae rates in patients treated with HBO_2 therapy (25% v. 46.1%; p=0.007).[48] The trial also found that pre-chamber cerebellar dysfunction was associated with cognitive sequelae (Odds ratio=5.71; 95 percent confidence interval=1.69 to 19.31; P=0.005). Even after correction for pre-chamber cerebellar dysfunction and stratification variables (age, loss of consciousness, time to chamber), HBO_2 therapy remained the more effective therapy (OR=0.45; 95-percent confidence interval=0.22 to 0.92;

P=0.03). Although not part of this study, the authors also reported that cognitive sequelae were less frequent in HBO_2-treated patients at 12-months, by intention-to-treat analysis (P=0.04) or, in only those patients with follow-up data (N=128; P=0.08). In this clinical trial, CO patients were treated with 3 HBO_2 treatments in 24 hours, because Gorman demonstrated that more than one HBO_2 session was better than one.[43] Additional methodological details of the trial by Weaver, et al. are available and re-affirm the validity of their results.[52] In addition, the magnitude of neuropsychological dysfunction exhibited by patients with cognitive sequelae in this trial was substantial.[52]

Currently, there is no clear consensus among hyperbaric practitioners as to the length of delay from poisoning beyond which there is little chance for benefit from HBO_2.[53] As clinical investigations involving neuro-imaging and neuropsychiatric assessment become more sophisticated, they seem to demonstrate that some cognitive and cerebral vascular abnormalities from CO that persist despite aggressive therapy.[23,48,53-56] Patients may exhibit persistent deficits although the incidence is lower with HBO_2 treatment.[46,48,57] In the randomized trial by Weaver, et al., more than 60% of enrolled patients were treated with HBO_2 in less than 6 hours following poisoning, so this trial is not powered to determine the maximal delay to HBO_2, yet still reduce 6-week cognitive sequelae.[48]

COHb level is not predictive as a risk factor for CO-mediated morbidity or mortality.[15-18, 38-42, 58] In some animal models, CO-mediated hypoxia, plus a decrease in perfusion due to an associated cardiovascular insult are required to precipitate CNS pathology,[2,3,21,29,59,60] yet loss of consciousness is not necessarily required for cognitive sequelae[61,62]. Exposure to relatively low levels of CO (50 to 90 parts per million for 60 minutes) has been demonstrated to cause vascular oxidative stress in animal trials.[1,63,64]

Sustaining cardiac injury at the time of CO poisoning confers a 2 to 3-fold increased risk for cardiovascular-related death in the ensuing 10 years after poisoning.[22] Therefore, careful assessment of cardiac injury at the time of poisoning is warranted, as is longitudinal follow-up of those identified as having cardiac injury.

Epidemiologic studies suggest that prognosis is poorer for patients who have underlying cardiovascular disease, are more than 60 years old, have suffered any interval of unconsciousness due to the CO poisoning, or demonstrate severe acidosis.[16,17] From a prospective study of 163 patients not treated with HBO_2, age $\geq$36 years or a CO interval exposure $\geq$24 hours increased cognitive sequelae risk.[65] The presence of pre-treatment cerebellar dysfunction is associated with cognitive sequelae,[48] and therefore may also be a justification for HBO_2 therapy. In this regard, it is important to recognize that HBO_2 can reduce 6-week cognitive sequelae in patients without initial cerebellar dysfunction (p=0.05).[48,52] When other indications are present the absence of cerebellar abnormalities should not dissuade a physician from using HBO_2.

A recent study suggests that patients lacking the apolipoprotein e4 allele have reduced cognitive sequelae if treated with HBO_2, where patients possessing the e4 allele do not.[66] The prevalence of the e4 allele in the US population is approximately 30%. Since the apolipoprotein genotype

will be unknown at the time a poisoned patient presents, HBO_2 remains a reasonable recommendation.

Patient Selection for HBO_2 therapy

If patients manifest signs of serious poisoning (e.g. transient or prolonged unconsciousness, neurologic signs, cardiovascular dysfunction, or severe acidosis) or if their age is ≥36 years, or if the carbon monoxide exposure duration interval is ≥24 hours (even if intermittent), referral for HBO_2 therapy should be initiated regardless of their COHb levels. Although COHb levels do not correlate with outcomes, it is reasonable to recommend HBO_2 for patients with COHb levels ≥25%.[67] The role of neuropsychological tests in evaluating acute injury or patient selection for HBO_2 therapy is not clear.[44-46,48,51,68,69] A majority of hyperbaric physicians use HBO_2 to treat patients with less severe symptoms when neuropsychological testing is abnormal or when the COHb levels are elevated to the range of 25-30%.[53] A consensus paper discusses acute CO poisoning, including recommendations for HBO_2 therapy and logical directions for future research.[69] Until objective predictive markers associated with a poor outcome are identified, recommendations for HBO_2 therapy are based on treatment of those with the greatest mortality and morbidity risks.

Clinical Management

The study by Weaver, et al. offers a standardized HBO_2 treatment protocol for acute CO poisoning.[48] In this protocol, patients were exposed to 3 atm abs oxygen for 25 minutes, 5 minutes air, 25 minutes oxygen, and 5 minutes air, followed by chamber depressurization to 2 atm abs. At 2 atm abs patients breathed 100% oxygen for 30 minutes, 5 minutes air, 30 minutes oxygen, then depressurized to atmospheric pressure. Supplemental oxygen was then provided, if necessary to maintain arterial oxygen saturations ≥90%. Two additional HBO_2 treatments are used in 6 to 12 hour intervals. These two treatments exposed patients to 2 atm abs oxygen for 30 minutes, 5 air, 30 oxygen, 5 air, then 30 minutes oxygen.[48] In the study by Thom, et al. the HBO_2 exposure protocol was treatment at 2.8 atm abs for 30 minutes followed by 2.0 atm abs for 90 minutes.[46] Poisoned patients should have an electrocardiogram and serial measurement of cardiac enzymes such as the creatinine kinase MB fraction and troponin I. If there is evidence of cardiac injury, further cardiac evaluation and follow-up is advisable.[22,59]

Even with HBO_2, some patients will develop cognitive or other neurological sequelae. Follow-up of poisoned patients and referral of those with sequelae to the appropriate resource is important.

Evidence-Based Review

The AHA level of evidence for HBO_2 in acute CO poisoning is A. This recommendation is based upon three supportive randomized clinical trials in humans and considerable evidence from animal studies.

Utilization Review

Determination of the optimal pressure and number of hyperbaric oxygen treatments will require additional study, as will the time following poisoning after which therapy is no longer effective. The majority of hyperbaric centers follow the dictum that all patients at high risk deserve a single treatment, with multiple treatments provided for those who fail to demonstrate full recovery upon completion of the first treatment. Weaver, *et al.* treated patients with hyperbaric oxygen three times within 24 hours,[48] and Gorman, *et al.* found that the cognitive sequelae relapse rate was lower in patients treated two or more times compared to once.[43] Efficacy of three HBO_2 treatments in the trial by Weaver, *et al.* has persuaded some practitioners to follow this protocol.[35]

In patients with persistent neurologic dysfunction after the initial treatment, subsequent treatments may be performed within 6-8 hours and continued once or twice daily until there is no further improvement in cognitive function. Utilization review is mandatory after the fifth treatment. The optimal dose of hyperbaric oxygen, that is to say the treatment pressure, cannot be clearly stated until mechanisms of injury and therapeutic actions of hyperoxia are better defined. Patients in the Weaver investigation received oxygen at 3.0 atmospheres absolute (atm abs), and two other randomized trials that found benefit for hyperbaric oxygen used at 2.5 atm abs and 2.8 atm abs.[44,46] Therefore, use of hyperbaric oxygen between 2.5 and 3.0 atm abs is appropriate.

Whether HBO_2 confers clinical improvement or a reduced rate of neurocognitive sequelae if administered beyond 6 hours from poisoning is unknown. Most hyperbaric oxygen practitioners do not offer HBO_2 when the interval from CO poisoning to HBO_2 is more than 24 hours.[35,69]

Cost Impact

The cost of HBO_2 as a primary therapy in CO poisoning is modest; however, prevention of morbidity from neurologic and cognitive sequelae represents a substantial cost savings to the health care system and society.

CO POISONING COMPLICATED BY CYANIDE POISONING

Rationale

Carbon monoxide and cyanide poisoning frequently occur simultaneously in victims of smoke inhalation.[70-76] In combination, these two agents exhibit synergistic toxicity.[77,78] HBO_2 should be strongly considered in such cases. In addition to its effect on CO, HBO_2 may have a direct effect in reducing the toxicity of cyanide[79-83] and in augmenting the benefit of antidote treatment.[84-86] Clinical reports involving the use of HBO_2 in pure cyanide poisoning are infrequent; however, some reports suggest a benefit.[87-89] Since the condition carries a high mortality risk, HBO_2 treatment is justified if standard therapy is unsuccessful. The traditional antidote for cyanide poisoning involves formation of methemoglobin through the infusion of sodium nitrite.[90,91] This treatment has the potential to impair the oxygen carrying capacity of hemoglobin. In the smoke inhalation victim, with concomitant COHb and possible pulmonary injury, there is an obvious added risk associated with methemoglobin formation. The HBO_2-mediated increase in plasma-dissolved oxygen content offers a direct benefit. However, one must be cautious in this setting because the methemoglobin level may be directly lowered by hyperoxia (at least at 4 atm abs), possibly reducing the efficacy of antidotal therapy.[92]

Antidotal therapies other than nitrite-methemoglobin formation exist, although their use is still investigational. Hydroxocobalamin and dicobalt EDTA directly bind cyanide, obviating the need for methemoglobin formation,[93,96] however, since these agents possess their own toxicities, their use is currently limited. Until direct antidotes become available, HBO_2 is recommended as an adjunct to the treatment of combined CO poisoning complicated by cyanide poisoning.

Evidence-Based Review

See CO poisoning above.

Utilization Review

The treatment protocol is the same as for CO poisoning.

Cost Impact

Since most patients with CO poisoning complicated by cyanide poisoning will receive only one to three treatments, the cost of HBO_2 for this condition is justifiable. In this serious condition, a reduction in mortality, and possibly morbidity, reduces health care cost.

Smoke Inhalation

Based on anecdotal clinical reports and controlled animal trials,[97-100] HBO_2 is of possible benefit for the pulmonary injury related to smoke inhalation. However, there is currently insufficient evidence to condone its use outside of an experimental protocol.

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