CARBON MONOXIDE POISONING

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Background :

Carbon monoxide (CO) is a colourless and odourless gas that results from the incomplete combustion of fuels. CO poisoning is still presently the primary cause of accidental poisoning in Europe and North America causing an estimated 50,000 emergency department visits in the United States annually (1), 4000 in England (2) and 1000 to 1500 clinically symptomatic CO poisoning in France (3). Moreover, all these data may be underestimated (4).

In Europe, most poisonings are accidental, even if self-attempt poisoning is not unusual (car exhaust in a closed room for example). Accidental CO poisoning can occur for multiple causes such as a blocked chimney, a faulty gas boiler, a barbeque inside a tent. Sources of carbon monoxide are numerous : boilers, gas fires, central heating systems, water heaters, cookers, open fires, wood burning stoves (5). Due to prevention efforts, CO poisoning incidence tends to presently lower. Many residence are now equipped with a CO detector. Emergency services such as firemen move in at home with detectors that can quickly diagnose poisoning. However, CO poisoning remains a public health problem.

On a clinical level, neurological and cardiac involvements are predominant in CO poisoning, and depend on both the level of CO in the breathed air and the duration of exposure. Initially, symptoms of CO poisoning are nonspecific. Neurologic symptoms gradually increase from headache, myalgia, dizziness, to neuropsychological impairment, confusion, loss of consciousness, and coma. Cardiac manifestations may also occur such as chest pain, myocardial infarction, and cardiogenic shock leading to death. (6) Chronic poisoning is characterized by fatigue, emotional problems and neurological abnormalities. (7)

Carbon monoxide poisoning is a clinical diagnosis based upon the presence of compatible symptoms and a history of exposure to CO (identified source of CO or elevated ambient CO levels). Exposure can be confirmed by an elevated carboxyhemoglobin (COHb) in the blood. However, the half-life of COHb is relatively short, particularly when breathing supplemental oxygen, and some CO-poisoned patients may have normal COHb levels at the time of evaluation (8). Carboxyhemoglobin can be measured by blood gas oximeter (spectrophotometer) from arterial or venous blood (9) or more recently by pulse CO-oximetry (10). In most of the clinical studies, the threshold used for diagnosing an exogenous CO exposure is at least 5% in non-smokers or 10% in smokers. But for epidemiological studies, an carboxyhemoglobin level over 3–4% in nonsmokers and over 6-8% in smokers can be considered outside the expected physiological range (8). However, if COHb level measurement is useful for the diagnosis of CO poisoning, the COHb level is not predictive as a risk factor for CO mediated morbidity or mortality (8).

Patients with CO poisoning should be immediately treated by normobaric oxygen (NBO) using a nonrebreather reservoir face mask supplied with high-flow oxygen, or by artificial ventilation with FiO2 100% during 8-12 hours. Supplemental oxygen inhalation will hasten dissociation of CO from hemoglobin and provide enhanced tissue oxygenation. All patients having been treated for acute accidental CO poisoning should be seen in clinical follow-up 1–2 months after the event. Patients with evidence of cardiac damage after poisoning should be referred for appropriate cardiac evaluation.

Late or evolving cognitive impairments including memory disturbances, depression, anxiety, inability to calculate, vestibular problems, and motor dysfunction may develop (8). Cognitive sequelae following CO poisoning are common. These late manifestations often occur in patients who have not received any oxygen treatment during the acute phase but may also be seen in patients having received NBO. Risk factors for neurologic sequelae at 6 weeks after CO poisoning are loss of consciousness, age of 36 years or more, and carboxyhemoglobin levels greater than or equal to 25%.

Lastly, it has been shown that, compared to the normal population, individuals surviving an episode of accidental CO poisoning have an increased long-term mortality rate, especially from cardiac events (11).

In pregnant women, CO poisoning exposes to an increased risk of miscarriage and fetal death in utero. Following the concentration gradient, CO passively crosses the placental barrier from the maternal to the fetal blood. Fetal HbCO level is 10 to 15% higher than in the mother due to the normal fetal low PO_2 and the fetal hemoglobin CO affinity higher than that of adult hemoglobin. Thus, CO fetal poisoning is much more severe than maternal poisoning.

Mechanisms of CO toxicity

CO poisoning is responsible of a global hypoxia caused both by a decrease in tissue oxygen delivery and and a direct cellular impairment of oxygen utilization. Re-oxygenation may induce additional injury due to increase in free oxygen radical production, immunological and inflammatory damage (8,12). From the Haldane time, CO induced tissue hypoxia is known to be the consequence of COHb formation (13) completed by an increase in hemoglobin oxygen affinity evidenced by a leftward shift of oxyhemoglobin dissociation curve (14)
More recently, cellular dysoxia has been shown to play an even more important role than the traditional Haldane explanation. Several mechanisms have been described (12) :

- CO binding to cellular hemoproteins (i.e., cytochromes a_3, myoglobin) and increased steady-state concentration of nitric oxide (15)
- Inhibition of cellular metabolism (16)
- Oxidative stress

The production of free oxygen radicals production due to the CO induced dysoxia is increased during the recovery phase when the animal breathe an insufficient O_2 pressure leading to :

- Activation of platelet adhesion molecules and platelet-neutrophil aggregation, resulting in neutrophil degranulation, release of myeloperoxidase, and endothelial cell oxidative stress
- Neutrophil adherence to vasculature, leukocyte immune response, and conversion of xanthine dehydrogenase to xanthine oxidase
- Lipid peroxidation of cell membrane
- Alteration in the structure of myelin basic protein and subsequent lymphocyte proliferation
- Excitatory neurotransmitter toxicity
- Activation of hypoxia-inducible factor-1alpha
- Neuronal necrosis and apoptosis

Rationale for HBO use

Since the work of Coburn, it is well known that COHb has an average half-life of 320 min in patients breathing normal room air at sea level, reduced to an average of 71 min in patients breathing normobaric oxygen (NBO) and an average of 21 min at 2.5 ata, 100% oxygen (17,18). This was the rationale supporting the first use of HBO for CO poisoning at the end of the 1950's years.
However, as the CO induced decrease in tissue oxygen delivery is no more considered as a sufficient explanation for CO toxicity, especially for its neurocognitive long term manifestations, hyperbaric oxygen (HBO) therapy has been extensively studied in experimental studies in order to further explains its mechanisms of action. Several effects have been shown (19,20) :

- Reversal of cytochrome a_3 binding
- Preservation of adenosine triphosphate production
- Adaptive/protective oxidative stress response through increased heme oxygenase-1

- Upregulation and modulation of various antioxidant enzymes
- Induction of heat shock protein, which protects against oxidative stress
- Reduced myeloperoxidase activity
- Reduced leukocyte adhesion
- Inhibition of immune response
- Blocking xanthine-dehydrogenase conversion to xanthine oxidase
- Prevention of brain cell membrane lipid peroxidation
- Muted adduct formation and blocked inflammatory response to altered myelin basic protein
- Decrease in hypoxia-inducible factor-1 expression
- Reduction of necrosis and protection against accelerated apoptosis

Animal studies have shown that only high oxygen pressure such as used in HBO favourably modulates CO effects. NBO or insufficient O_2 pressure do not. In clinical practice, the dose of HBO is not known. But in negative clinical studies, a low dose (2 ata) was used contrasting with positive studies where the dose was higher. Only the least possible delay allows optimal benefit.

Evidence

Since HBO was first used as a treatment in CO poisoning in the late 50's, guidelines have been developed on the basis of clinical experience. Numerous uncontrolled studies have reported lower mortality and morbidity in CO poisoned patients treated with HBO (8,21–26). In the late 80's HBO came under criticism due to the lack of prospective controlled studies supporting its use in CO poisoning

This last 20 years, 7 prospective randomized trials comparing HBO to NBO in CO poisoning with conflicting results. Of these 7 trials, 4 demonstrated better clinical outcome among patients receiving HBO while 3 showed no effect. (27–32)

The first randomized study by Raphael et al (29) included 343 patients without loss of consciousness, treated either by HBO (2 ata for 60 min) or NBO (1 ata for 6 hours). There were no significant differences in persistent neurologic manifestations at one month after poisoning. A negative conclusion was also drawn from a second trial enrolling 286 patients with loss of consciousness treated with one or two HBO sessions. This study may be criticized for using overly broad inclusion criteria; an inadequate HBO regimen; inappropriate time of assessment; and unsuitable outcome measures. The same study group conducted a similar study that enrolled 385 CO-poisoned patients over 11 years. (27) wit a similar HBO protocol. In patients without loss of consciousness, recovery rates were similar between groups (58% vs. 61%). In patients with loss of consciousness, recovery was lower in those receiving two HBO sessions compared to one HBO session (47% vs. 68%). But, the same critics than for the previous one may be opposed, especially for the. HBO protocol which was under-dosed (2 ata). Animal studies have shown a 2 ata oxygen pressure may not promoted recovery of mitochondrial metabolism (34). A partial pressure of oxygen greater than 2 ata is required to achieve maximum inhibition of adhesion molecules in human polymorphonuclear leukocytes (35). This latter mechanism is an important HBO related beneficial property modulating CO-mediated oxidative injury (36).

The studies by Ducasse et al. and Thom et al. were both prospective, randomized clinical trials involving treatment at 2.5–2.8 ata within six hours of poisoning, and both studies found significantly better outcomes with HBO than NBO. (30,31) The lack of blinding potentially limits the level of evidence of these studies. An other positive randomized controlled trial has been published but only as an abstract.

A blinded, randomized clinical trial from Australia demonstrated that HBO therapy did not improve outcome at hospital discharge (approximately three days after poisoning) as compared to 3 to 6 days of NBO (32). Certain methodological problems flaw the interpretation of its findings: no cognitive evaluation at one month, high number of patients lost for follow up. Cluster randomization was used, no intention-to-treat analysis was performed, and no distinction between post-traumatic stress syndrome, depression, and cognitive dysfunction was reported. But the major problem of this study is the lack of clinical relevance: Neither the NBO group nor the HBO received standard oxygen treatment.

A double-blind randomized clinical trial demonstrated an impressive reduction in six week neuropsychological sequelae rates in patients treated with HBO (28) Intervention group was treated within a 24-hour period, by three HBO (3 ata, 2 ata, 2 ata) and control group by one NBO plus two sessions of exposure to normobaric room air. Cognitive sequelae at six weeks were less frequent in the hyperbaric-oxygen group (19 of 76; 25.0%) than in the normobaric-oxygen group (35 of 76; 46.1%, P=0.007). Cognitive sequelae were less frequent in the hyperbaric-oxygen group at 12 months, according to the intention-to-treat analysis (P=0.04). Methodologic quality of this study is high and only few critics may be made.

In summary, within these 7 randomized controlled trials, 3 are negative but may be discarded because of an insufficient dose of HBO for one and the non clinical relevance for the other. Within the 4 positive studies, the Weaver et al. study is of a high methodological quality. Due to the difference in the methodological quality of the 6 studies, to perform a meta-analysis as done in the Cochrane's review exposes to a major bias and cannot rebut the conclusion of the Weaver's study..

Patients selection for HBO

CO poisoned patients must be immediately treated with NBO as a first aid treatment
HBO Therapy is recommended in patients with diagnosed CO poisoning when at high risk of immediate or long term complications.
High risk includes:
- Unconsciousness at or before admission
- Clinical neurological, cardiac, respiratory or psychological symptoms or signs
- Pregnant women

Treatment delayed beyond 24 hours after the last exposure to CO is not recommended if the patient has become symptom-free.
In CO poisoned patients not at high risk, there is a choice between normobaric oxygen therapy for 12 hours and HBO. Until the results of further randomized studies are available, HBO remains optional in these patients.

Current protocol

Taking into account the study's results of Raphael et al, HBO dose have to be between 2.5 and 3 ata. While the majority of hyperbaric centers treat with a single HBO session, the best evidence for reduced cognitive sequelae after CO poisoning is for three HBO treatments within 24 hours. The optimal time to treat by HBO CO poisoning is unknown. But animal and clinical data favor a delay less than 6 hours between cessation of CO exposure and beginning of HBO session.

Cost impact

The cost of HBO_2 as a primary therapy in CO poisoning is modest when compared to the cost of avoided neurologic and cognitive sequelae. This represents a substantial cost savings to the healthcare system and society.

Proposals for recommendations with a high quality of evidence

Oxygen High volume should be administered as soon as possible, once a CO poisoning is suspected. At the scene of poisoning, oxygen should be administered by a high flow (12-15 l / min in adults) or with the use of tracheal intubation and controlled ventilation with FiO 2 = 1. The patient must be evacuated to the hospital for examination. HBO Therapy is recommended in patients with diagnosed CO poisoning when at high risk of immediate or long term complications (High risk includes: unconsciousness at or before admission, Clinical neurological, cardiac, respiratory or psychological symptoms or signs, Pregnant women). HBO dose have to be between 2.5 and 3 ATA. When indicated, NBO therapy should be applied during at least 8 to 12 hours.

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Recommendations :

1 We recommend 100% oxygen to be apply immediately to any carbon monoxide poisoned person as a first aid treatment (Type 1, level C).

2 We recommend HBO for every carbon monoxide poisoned person who presents consciousness alteration, clinical neurological, cardiac, respiratory or psychological signs whatever its carboxyhemoglobin level at hospital admission (Type 1, level B).

3 We recommend HBO in pregnant women poisoned by carbon monoxide whatever her clinical presentation and carboxyhemoglobin level at hospital admission (Type 1, level B).

4 We consider reasonable to treat either by 12 hours normobaric oxygen or HBO patients with minor carbon monoxide poisoning (Type 3, level B).

5 We recommend not to treat by HBO asymptomatic patients seen more than 24 hours after the end of carbon monoxide exposure (Type 1, level C).

Fire smoke poisoning

Rationale

Aside its effects on the respiratory track, fire smoke inhalation causes a double systemic poisoning: CO and cyanide. In combination these two agents exhibit synergistic toxicity. Severe cyanide poisoning is rapidly fatal; symptoms of mild or moderate cyanide exposure can be similar to that of CO poisoning and include headache, nausea, confusion, altered mental status, and cardiac problems. Cyanide poisoning is difficult to highlight biologically and so, emergency treatment has to be administer when strongly clinically suspected without waiting for laboratory confirmation. A CO poisoning complicated by cyanide should be considered in patients presenting from fires who manifest altered mental status and those patients with soot in the mouth or mucous membranes. However, because CO is the predominant component in fire smoke, these patients should always be considered as CO poisoned if cyanide poisoning is treated.

Once in the body, like CO, cyanide binds to the enzyme cytochrome c oxidase and blocks production of adenosine triphosphate. The result is cellular hypoxia and metabolic acidosis. Patients with cyanide poisoning often require life support measures such as assisted ventilation, supplemental oxygen, and blood pressure support. The antidote of choice is hydroxocobalamin, but on a pathophysiological basis, HBO could be of benefit in cyanide poisoning as it is known to preserve ATP production. These two poisonings should be treated together according to their own specific protocol without favoring one over the other.

However, in fire smoke poisoning, respiratory injury is also present and may be sometimes predominant. HBO indication has to be discussed in term of benefit/risk balance in patients presenting with ARDS and should only be performed in hyperbaric centers well equipped and trained to treat critical care patients.

Evidence-Based Review of HBO for Cyanide Poisoning

There are no controlled clinical trials examining HBO for pure cyanide poisoning. In combined CO-Cyanide poisoning due to fire smoke inhalation, just a few reports suggest a benefit (37,38). In those patients, most of the time, HBO is indicated for the CO poisoning and it is difficult to attribute the favorable outcome to its effect on CO and/or cyanide poisoning.

Recommendations :

We recommend HBO indication in CO poisoned patients due to fire smoke inhalation is based on the same criteria than for CO intoxication from other origin. Associated cyanide poisoning should be treated according to its specific protocol. (Type 1, level C).

Study (authors, year)	Type	Nb patients	Aim(s) / Evaluation criteria	Inclusion / Exclusion criteria	HBO protocol (pressure, time, nb of session)	Results	Conclusion / comment
Raphael, 1989	Randomized study A	343	Neuropsychiatrics manifestations at one month	Accidentally poisoned by CO at home. No initial loss of consciousness	2 ata/2 hours versus 6 h of NBO	HBO had no advantage over NBO in the treatment of patients without loss of consciousness.	No benefit of HBO but Insufficient dose of HBO and late treatment (>6 hours)
Raphael, 1989	Randomized study B	286	Neuropsychiatrics manifestations at one month	Accidentally poisoned by CO at home. Initial loss of consciousness	One session of HBO (2 ata/2 hours) versus two sessions of HBO (2 ata/2 hours)	For patients with initial loss of consciousness two HBO sessions had no advantage over one session.	No benefit of two sessions of HBO
Mathieu, 1996	Randomized study	575	Neurologic manifestations at 3 months	CO poisoned without coma	One session of HBO (2.5 ata during 90 min) versus NBO	Fewer persistent neurologic manifestations at 3 months in HBO group	Benefit of HBO
Thom, 1995	Prospective, randomized, nonblinded comparative trial	65	Delayed neurologic sequelae	Patients with symptomatic acute carbon monoxide poisoning	HBO at 2.8 ata for 30 minutes (within a 6-hour period), followed by 2.0 ata for 90 minutes; or NBO until all symptoms resolved	HBO treatment was associated with significant reduction in the incidence of delayed neurologic sequelae	High level of evidence in favour of HBO
Ducassé, 1995	Prospective, randomized, open, blinded evaluation	26	EEG, Cerebral blood flow	Moderate acute CO poisoning	HBO at 2.5 ata for 120 minutes versus NBO during 10 hours	HBO reduces the time of biological and clinical recovery in non-comatose patients	Primary endpoint not relevant
Scheinkestel, 1999	Randomized, controlled, double-blind trial	191	Neuropsychological performance at completion of treatment, and at one month where possible	All patients referred with CO poisoning	HBO at 2.8 ata for 60 minutes versus NBO during 3 successive days	HBO therapy did not benefit the outcome	All type of CO poisonning
Weaver, 2002	Double-blind, randomized trial	152	Cognitive sequelae at 6 weeks	Patients with symptomatic acute carbon monoxide poisoning	Within a 24-hour period, consisting of either three HBO (3ata, 2ata, 2ata) or one NBO plus two sessions of exposure to normobaric room air.	Cognitive sequelae at six weeks were less frequent in the HBO group than in the normobaricoxygen group	High level of evidence in favour of HBO
Annane, 2011	Randomized controlled trial A	179	Complete recovery at 1 month	Accidentally poisoned by CO at home No initial loss of consciousness	HBO at 2 ata for 60 minutes versus NBO during 6 hours	No difference in 1-month complete recovery rates with or without HBO	Insufficient dose of HBO Lot of lost to follow-up
Annane, 2011	Randomized controlled trial B	206	Complete recovery at 1 month	Accidentally poisoned by CO at home With initial loss of consciousness	either 4 h of NBO plus one HBO session (2 ataA) or 4 h of NBO plus two 2 HBO sessions (2 ata)	Complete recovery rates were significantly lower with two than with one HBO session	Insufficient dose of HBO Lot of lost to follow-up