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Invited Review CHILD HEALTH AND DISEASES

Epidemiology, pathophysiology, clinical evaluation, and treatment of carbon monoxide poisoning in child, infant, and fetus

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ABSTRACT

Carbon monoxide (CO) poisoning is one of the most common types of poisoning causing death worldwide. In our country, it occurs particularly during winter as a result of leak from stove or water heater, or as result of inhalation during a fire. Although most poisonings occur accidentally, some cases are suicide attempt. As CO is a substance that is not visible and has no taste or smell and is therefore difficult to detect, the gas can be a "silent killer" that is not noticed until effects develop. CO reacts with oxygen, creating carboxy hemoglobin (COHb), which leads to tissue hypoxia. In addition, it has direct effect of causing cellular damage. Although symptoms of acute poisoning are most commonly observed in patients admitted to emergency rooms, effects of chronic exposure to CO can also seen. Clinically, although it affects all organ systems, involvement of central nervous system (CNS) and cardiovascular system is predominant. Most common poisoning symptoms are weakness, dizziness, headache, nausea, and nonspecific flu-like symptoms, like vomiting. Depending on severity of exposure, seizures, syncope, and arrhythmia may also be observed. In pregnant women, fetus can be harmed with relatively low level of COHb. Poisoning in infants has a more severe course than seen in other age groups. Symptoms must be associated with cause of poisoning, and careful anamnesis and treatment must be conducted quickly. Oxygen is the antidote for CO. It is administered through a mask in the form of normobaric oxygen therapy or through specific devices in the form of hyperbaric oxygen therapy. In this review, clinical data and current diagnostic and therapeutic approaches concerning CO poisoning are discussed.

Keywords: Carbon monoxide; child; fetus; hyperbaric oxygen; infant; poisoning, pregnant.

CO is a colorless, odorless, tasteless, non-irritating gas present in the environment even when there is no fire or smoke. It has been reported to be the most frequent cause of fatal poisoning, with an incidence rate of 31%. Average of 4% to 10% of all cases of poisoning occur during childhood, and 58% to 75% of deaths due to poisoning are caused by CO inhalation. In cases of poisoning by industrial chemicals, CO is the most common (11%) after inhalation of thinner (31%). In our country, CO poisoning is most frequently seen during winter months, especially during windy weather, as

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accident in the home due to inappropriate heating methods [1–3]. In the USA, third most frequent cause of accidental death is CO poisoning, most of which (57%) were due to inhalation of exhaust gases [4, 5].

Sources of CO

1) Endogenous production: CO is produced endogenously as result of human metabolism of hemoglobin. It functions as neurotransmitter, and it is produced at very low (0–5%) levels in every individual. In infants (3–7%), smokers, and patients with hemolytic anemia (5–10%), level is higher. Under physiological conditions, it saturates approximately 0.5% of hemoglobin, and it is known as COHb [6].

2) Hydrocarbons: CO is produced as result of incomplete burning of compounds with carbon component, such as coal, wood, petroleum, fertilizers, dried dung, and natural gas. Concentration in the atmosphere is generally less than 0.001%; however, when there is incomplete combustion of hydrocarbons, ratio in the atmosphere increases. Such pollution is greater in air of urban environment [7].

3) Exhaust Gases: Exhaust gases emitted from motor vehicles are major deadly source of CO. Exposure to gases released in closed garage may lead to fatal blood level of CO within 10 minutes. Potentially fatal exposure may also occur in semi-closed garage or areas adjacent to garage [7, 8]

4) Fire: CO is liberated in burning of any material [7].

5) propane and methane: Incomplete combustion of gases generates CO. Leaks from poorly maintained or improperly used heating systems can be a source, as well as petrochemical industry use of natural gas and crude oil [7].

6) methylene chloride: Vapor of methylene chloride, component of thinners and other solvents, penetrates the skin, is inhaled through the lungs, and transported to the liver via blood circulation, where it is metabolized, resulting in release of CO [7].

7) cigarette smoke: Cigarette smoke is 4% CO. Baseline COHb level in smokers and nonsmokers living in metropolitan cities have been detected at 10% and 2%, respectively [6, 8].

Pathophysiology of co poisoning

CO gas is readily absorbed and is unchanged by the lungs. After absorption, it largely (90%) binds to hemoglobin, and rarely (10%), to myoglobin and cytochrome C-oxidase. Less than 1% is dissolved in plasma, and less than 1% of CO is oxidized to carbon dioxide. Cardiac injury has been associated with hypoxia in human and animal studies, and it has been reported that neurological and perivascular injuries were hypoxic as result of oxidative stress (reoxygenation) secondary to CO exposure. Damage to central nervous system (CNS) as result of hypoxia may lead to cardiovascular insufficiency, and effect of high doses of CO on smooth muscle may result in hypotension [7, 9, 10].

How does CO induce cellular injury?

A. It impairs both oxygen carrying capacity of blood and oxygen diffusion.

1. CO diffuses into hemoglobin. CO demonstrates 200-fold stronger affinity for hemoglobin compared with oxygen. In event of poisoning, CO and oxygen compete to bind to hemoglobin, and CO wins the contest. Therefore, even small increase in CO level may cause poisoning (Haldane effect) [7].
2. It prevents delivery of oxygen to tissues via hemoglobin. Since CO binds to hemoglobin with higher affinity than oxygen, a shift occurs in oxygen-hemoglobin dissociation curve, making it a hyperbola. With this shift, capacity of hemoglobin to deliver oxygen to tissues decreases, with resultant development of tissue hypoxia [6].

B. CO has direct effect of causing tissue injury.

Binding of CO to hemoglobin does not explain all pathophysiological effects seen in CO poisoning. Observations in various animal studies suggest that direct effect of CO on cells is more important than decrease in oxygen carrying capacity of hemoglobin [11].

1. CO impairs normal respiratory function of cells. CO irreversibly binds to hemeproteins (cytochrome a-3 and myoglobin), which carry oxygen within the cell, resulting in cellular respiratory dysfunction. As a consequence, there is mitochondrial deterioration in CNS and heart cells, which require higher level of energy, cellular damage, and eventually tissue damage. Though mito-

chondrial functions improve with oxygen therapy, cellular damage cannot be recovered [6, 12].

2. CO causes myocardial injury by binding to cardiac myoglobin. CO binds to myoglobin with an affinity 60 times stronger than that of oxygen. Binding of CO to cardiac myoglobin induces myocardial depression, hypotension, and arrhythmias. Cardiac dysfunction developing secondary to CO poisoning further aggravates tissue hypoxia in a vicious cycle [7, 13].
3. CO induces re-oxygenation injury in CNS [9].
4. CO promotes formation of oxygen free radicals. CO causes hypoxia, which induces production of oxygen free radicals, resulting in reversible demyelinization in brain [7, 14, 15].

Clinical findings in co poisoning

Fetus, infant, children, the elderly, patients with cardiovascular disease, anemia, pulmonary disease, and pregnant women are at higher risk in event of CO poisoning compared with other patients. Clinical severity of CO poisoning depends on amount of CO in the inhaled air, duration of exposure to CO, and general state of health of the affected individual. Although CO poisoning is harmful for all systems, most frequently CNS and cardiovascular systems are affected. Neurological findings are clearly defined; however, data related to cardiac pathologies, especially in children, are limited in number, and such pathology can be difficult to recognize. Myocardial injury may develop without any systemic symptom. Most frequent cause of death in CO poisoning is cardiac arrest secondary to ventricular arrhythmia. Clinical findings differ between cases of acute and chronic poisoning [8, 12, 16, 17].

Symptoms of poisoning based on cohb level [18]

- 10–20%: Nausea, fatigue, tachypnea, emotionality, confusion, clumsiness
- 21–30%: Headache, exertional dyspnea, angina, visual impairment, some insufficiency in adaptation to environment, inadequate reaction to danger, slight muscular weakness, and decreased sensory perception
- 31–40%: Dizziness, confusion, nausea, vomiting, visual impairment, problematic decision-making
- 41–50%: Fainting, changes in state of consciousness, amnesia, tachycardia, tachypnea
- 51–60%: Seizures, coma, severe acidosis
- ≥60%: Death

Symptoms of acute poisoning: Fatigue, severe headache, dizziness, nausea, vomiting, chest pain, palpitations, exertional dyspnea, attention deficit, imbalance, numbness, seizures, coma, respiratory arrest [19].

Findings of late-term poisoning: Rhabdomyolysis, non-cardiogenic pulmonary edema, multiorgan failure, disseminated intravascular coagulation, acute tubular necrosis, incontinence, mutism, mask-like face, and delayed neuropsychiatric manifestations [20].

In 30% of cases with nonspecific symptoms of CO poisoning, diagnosis is overlooked. Patients may be misdiagnosed with flu, gastroenteritis, or infantile colic [7]. In moderately severe acute CO poisoning, nonspecific symptoms, such as tachycardia, tachypnea, headache, nausea, vomiting, and lethargy, may be confused with viral infections [16]. It becomes even more difficult to make distinction during winter months. Thorough anamnesis may reveal exposure to CO; however, many mild cases of poisoning go undiagnosed, and late-term deaths can occur due to CO poisoning [12].

In patients who are chronically exposed to low dose of CO, headache, lassitude, thought disorders, dizziness, paresthesia, chest pain, palpitation, visual impairment, nausea, diarrhea, and abdominal pain may be noticed. In children, school performance may worsen, and these symptoms may be frequently confused with those of other diseases. In cases of chronic poisoning, it should be remembered that clinical picture may worsen, and signs and symptoms of acute phase may develop [8, 12].

After resolution of symptoms of acute poisoning, delayed neuropsychiatric syndrome manifests in nearly 20% of patients within 3 to 240 days (frequently within first month). In these patients, neuropsychiatric disorders, such as dementia; memory deficit; personality changes; learning difficulties; behavioral, attention, and concentration disorders; psychosis; parkinsonism; paralysis; chorea; apraxia; peripheral neuropathy; or incontinence may be observed [7]. No clinical or biochemical markers can

determine the patients at risk for this syndrome; however, symptoms of 60% of patients with delayed neuropsychiatric syndrome regress within 1 year. This condition is more frequently seen in adults [21].

Diagnosis and clinical evaluation in co poisoning

History: Clinical suspicion is the most important step in the diagnosis. Environmental conditions, heating systems, defects in heating systems, maintenance of system, extent of fire (if any), duration and intensity of exposure to CO, number of individuals affected, presence (if any) of sick animals exposed to CO, extent of exposed area, and time of admission or referral to hospital should be investigated during anamnesis [7, 12]. Relatives of unconscious children should be questioned for differential diagnosis, and information about any comorbid systemic disease (especially cardiopulmonary and hematological diseases) of the patient should be obtained. All of this information is important to determine diagnosis and prognosis [5].

Physical examination: Vital signs and symptoms should be evaluated first. Tachycardia, tachypnea, slight increase in blood pressure, and hyperthermia may be seen, and as severity of poisoning increases, bradycardia, hypotension, and hypothermia may occur. Complete systemic examination should be performed. Findings related to differential diagnosis should be investigated, and after stabilization of the patient, detailed neurological examination should be performed. If possible, the patient should be requested to walk to determine balance disorder. Cherry-red color of skin and mucosal layers, suggested as classic pathognomonic sign of CO poisoning, has no diagnostic value, as it is only seen post mortem. Bullae, vesicles, and erythematous spots may, however, be seen on skin surface. Cardiac auscultation should include exploration for dysrhythmia, and pulmonary examination should include signs of respiratory distress and pulmonary edema [7, 8, 12, 22].

Fundoscopic examination: In severe cases of CO poisoning, papilledema, optic atrophy, flame-shaped hemorrhage in retina, bright red veins (early sign), and enlargement of retinal veins may be detected. Visual field defects (central scotoma, homonymous hemianopsia, blindness, and retrobulbar neuritis) should be evaluated.

Laboratory: Biochemical analyses: Abnormal renal or and hepatic function test results, hyperglycemia, elevated anion gap, hypokalemia, or elevated levels of creatinine kinase, and cardiac enzymes, such as troponin-I and creatinine kinase-MB, may be seen. Hemogram may reveal slight degree of leukocytosis, and thrombocytopenia or prolongation of coagulation time may also be detected. PaO_2 remains at normal level. In mild degree of poisoning, respiratory alkalosis may be observed, and in case of severe poisoning, metabolic acidosis or lactic acidosis may be seen. Even if COHb values are within normal limits, increased serum lactate level is better indicator of tissue hypoxia. Complete urinalysis may reveal proteinuria or glucosuria. Severe poisoning may lead to myoglobinuria, albuminuria, oliguric or non-oliguric renal failure. As part of differential diagnosis, toxicological analysis for other poisons should be also performed [7, 9, 12, 23, 24].

Diagnosis: Diagnosis is based on percentage of COHb in the blood. Unconscious children presented with suspected undiagnosed CO poisoning should have COHb measured as soon as possible. In assessment of COHb, it should be remembered that baseline level in smokers is higher, and that if the patient was brought to the emergency service late and received even small quantity of oxygen during transport, COHb level may be underestimated. Clinical data should constitute basis of diagnosis. Strong correlation between severity of poisoning and COHb level does not exist; however, COHb percentage can be used to monitor treatment. Elevated level is important for diagnosis and monitoring, but lower level does not rule out diagnosis. Venous or arterial blood sample may be used to gauge level of COHb; however, arterial blood is preferred. COHb level below 10% is normal. Diagnosis of CO poisoning can be made if it is above 10% [7, 12, 17, 25]. In cases of CO poisoning, although blood oxygen levels are below normal, PaO_2 in blood gas remains within normal limits. If PaO_2 is below normal, then it is associated with "concomitant pulmonary dysfunction." Oxygen saturation is monitored with pulse oxymeter. However, since pulse oxymeter will absorb oxyhemoglobin and COHb in equal proportions, measured value represents sum. It should not be forgotten that falsely normal concentration may be displayed. Increased level of serum lactate, which should be measured in patients with metabolic aci-

dosis, indicates long-term exposure to CO [12, 26].

Electrocardiogram (EKG): EKG should be obtained for all cases. Though inadequate data are available for children, in nearly 35% of patients, signs of CO poisoning are observed on EKG. Frequently, myocardial lesions are observed; however, these lesions are fatal in less than 5% of patients. Ischemic changes, such as ST depression or ST elevation may be present on EKG. If ST elevation is seen, thrombolytic treatment is not suitable, since cause of cardiac ischemia is not thrombotic occlusion of coronary arteries, but instead, related to myocardial injury caused by direct effect of CO. Although arrhythmias that affect hemodynamic status are rarely seen, dysrhythmias, including ventricular extrasystoles and ventricular fibrillation can be detected [27, 28].

Chest X-ray: Aspiration pneumonia, pulmonary edema, and acute respiratory distress syndrome may be observed [19].

Computed tomography (CT) and magnetic resonance (MR) imaging: Cerebral CT should be performed in acute case for differential diagnosis of impaired consciousness. It is not used for diagnosis of CO poisoning. Normal cerebral CT may be associated with favorable clinical entity, though signs detected on CT may not be consistent with clinical findings [7]. Most frequently observed signs on CT within the first 6 hours include low-density lesions on the globus pallidus and deep white matter lesions secondary to damaging effects of CO mediated by oxygen free radicals [29, 30]. Similarly, as more sensitive imaging modality, MR image may be used. In delayed neuropsychiatric disease, bilateral necrosis of the globus pallidus and involvement of the cerebral cortex, hippocampus, and susbstantia nigra have frequently been demonstrated on CT and MR images [7, 30].

When to use CT/MR imaging [29–31]:

1. In differential diagnosis of acute loss of consciousness
2. In patients who have not recovered completely following hyperbaric oxygen (HBO) therapy
3. In cases of delayed neuropsychiatric disease
4. In infant

EKG: Slow, diffuse, low-voltage waves may be detected [23].

Differential diagnosis in co poisoning

In the differential diagnosis of CO poisoning, viral infections of the upper respiratory tract, hypoxic encephalopathy, encephalitis, meningitis, intracranial CNS pathologies, gastroenteritis, drug overdose (sedatives, hypnotics, salicylates), ethanol or methanol intoxication, cyanide intoxication, methemoglobinemia due to opiate use, migraine, hypertension headache, trauma, depression, and other psychiatric disorders should be taken into consideration [32].

Hospitalization criteria

Signs and symptoms persisting up to 4 hours after initiation of treatment, COHb level of more than 25%, signs demonstrating myocardial involvement, pregnancy, treatment-refractory metabolic acidosis, seizures, syncope, rhabdomyolysis [17, 32].

Criteria for home discharge after first aid

In the absence of hospitalization criteria, or if there is resolution or lack of complaints or signs after 4 hours of observation, child may be sent home. If consultation with pediatric psychiatry has ruled out possibility of suicide attempt, child may be discharged [17, 33]. At time of discharge, the patient should be informed about long-term effects of poisoning, and bed rest should be recommended to decrease oxygen consumption. In addition, any activity that may trigger anxiety should be avoided. Furthermore, patients should be warned against smoking and being in areas where others are smoking [17, 33].

Co poisoning in pregnant women and effect on fetus

Pregnant women poisoned with CO should be hospitalized and fetal monitoring should be provided. Affinity of CO to hemoglobin is stronger in fetus compared with other age groups. In event of CO poisoning, fetal COHb level will be higher than that of mother, and clearance is 5 times slower [34, 35]. Fetal COHb value returns to normal level 40 hours after COHb level normalizes in mother [7, 12]. It should not be forgotten that fetal involvement can occur even if maternal CO level is not toxic. Therefore, when compared with other cases of CO poisoning, HBO treatment is initiated at lower maternal CO level in pregnant women, and

is more aggressive and longer lasting in order to protect the fetus. No correlation has been determined between fetal death and maternal COHb level [27]. Nonetheless, CO exposure may have teratogenic effects of physical deformity, psychomotor disability, or miscarriage. Despite administration of HBO, in cases of CO poisoning during third trimester, adverse effects on fetal brain have been reported [18, 35].

Co poisoning in infants

Data are scarce concerning the application of HBO treatment for fetuses, infants, and pediatric patients [14]. In the literature, CO poisoning in neonates is usually reported in case where mother has also been exposed [36]. In infants, normal CO level is 4%. Immature CNS, higher affinity of CO to fetal hemoglobin compared with adult hemoglobin, longer half-life of fetal COHb, and greater consumption of oxygen increase risks of CO poisoning in infants [37]. American Academy of Pediatrics reported that use of CO detectors is useful to prevent exposure to CO in areas where there is cigarette smoke and where scented candles or incense are burned [38]. In the very few studies available, case reports have emphasized that oxygen treatment lowers COHb level more slowly in infants than in other age groups [39, 40].

Treatment of co poisoning

First goal in treatment of CO poisoning is to remove the patient from toxic environment and to deliver oxygen therapy to reverse cellular metabolic dysfunction. Vital functions should be ensured, vascular access should be established, and continuous cardiopulmonary monitoring should be performed. Treatment for tissue hypoxia and hypovolemia should be initiated, and if necessary, HBO therapy should be administered. If present, complications should be treated [12]. Rapid intervention and delivery of appropriate dose of oxygen constitutes basis of treatment since there is competition with oxygen to bind with hemoglobin, and because binding of CO to hemoglobin is reversible [27]. Half-life of CO is approximately 5 hours in room air, and 1½ hours in 100% oxygen environment, and 25 minutes during HBO treatment under 3 bar pressure. In other words, oxygen shortens half-life of CO. This has important implications for cardiac functions [40].

Oxygen treatment delivered with mask under normal pressure (normobaric oxygen therapy):

Oxygen should be delivered with airtight mask that closely adheres to the face at rate of 10–15 L/min until clinical symptoms resolve or COHb level drop below 5% (in case with cardiovascular or pulmonary symptoms <2%), typically average of approximately 4 to 6 hours. If the patient is unconscious or rescued from a fire, endotracheal intubation or mechanical ventilation may be required. Need for HBO should be evaluated [12, 27, 40]. Since lactic acidosis facilitates penetration of oxygen through tissues, it should not be corrected unless pH drops below 7.15 [7, 8].

Hyperbaric oxygen therapy: HBO therapy shortens half-life of COHb, reduces production and level of oxygen free radicals, inhibits lipid peroxidation, and improves impaired mitochondrial functions and platelet aggregation in capillaries. HBO therapy offers shortened symptom recovery time, decreased mortality rate, and development of fewer neuropsychiatric symptoms in the long term in comparison with use of normobaric oxygen. If patient has stable clinical status and is conscious but has history of loss of consciousness before admission, HBO therapy can be administered once. As indicated in the literature, these patients have higher risk of experiencing neuropsychiatric symptoms in long term, and HBO therapy decreases this risk. Beneficial effects of HBO therapy have been demonstrated even after 3 weeks in patients with persistent neuropsychiatric symptoms who didn't receive HBO therapy at baseline. However, since CO induces hypoxia and because there is direct cell injury as well, results of HBO therapy as far as late-term sequelae and mortality should be discussed further [8, 10, 12, 21]. If possible, HBO therapy should be performed within first 6 hours of poisoning. If after HBO therapy, loss of consciousness persists, therapy should be repeated within 6 to 8 hours. Prognosis improves after repeated applications. Delivery of 100% oxygen for 30 to 90 minutes under 2.7 to 3 ATA is recommended. Then, pressure is decreased, and 100% oxygen is delivered under 2.2 ATA for 90 minutes. HBO therapy may be repeated for patients whose symptoms do not regress [10, 17].

HBO indications in CO poisoning [7]**:**

1. Loss of consciousness (even transient)
2. Visual impairment
3. Every patient, at any age, if COHb >25–40%
4. In patients with ischemic heart disease, if COHb >20%
5. In infants, children, and pregnant women, if COHb >15%
6. Signs of cardiac ischemia or arrhythmia on EKG
7. Any clinical finding persisting for more than 3 weeks
8. Persistence of clinical symptoms despite normobaric oxygen therapy for 4 hours

Conditions where HBO therapy is contraindicated: Untreated pneumothorax is considered absolute contraindication for HBO treatment. HBO is not preferred for patients who received prolonged cardiopulmonary resuscitation, hemodynamically unstable patients, or patients with emphysema and/or chronic bronchitis [9, 24].

Possible side effects of HBO therapy: Rupture of tympanic membrane, ear discomfort, tension pneumothorax, hypotension, dysrhythmia, seizure, and oxygen toxicity may occur, and there is risk associated with transportation of unstable patient to therapy location [9, 24].

Other treatment modalities: In hypotensive patients, first hydration is performed, and if vasopressor is required, dopamine is usually preferred. If refractory hypotension is present, then noradrenaline is added to treatment [25]. For seizures, initially, benzodiazepines are administered. If the patient does not respond to treatment or if there is recurrence, other antiepileptics may be added, such as phenobarbital. If hemoglobin level is less than 10 g/dL, supportive treatment to correct anemia may be considered. Bed rest and reduced consumption of oxygen are advised; any anxiety-inducing activity should be avoided. Urine excretion rate should be 1 mL/kg/h. Some publications have indicated that hypothermia delays cortical cell damage, or even precludes neuronal injury and it may be used in treatment of CO poisoning [41–43].

Preventing co poisoning

Especially during winter months, public service messages broadcast in mainstream media should emphasize dangers associated with CO and advise about proper heating procedures for home and workplace, exhaust gases, petrochemicals, thinners, and fire. Greater regulation and oversight of employee health and safety is also needed. Efforts should be made to include Syrian war refugees currently residing in Turkey in these awareness-raising campaigns.

CO poisoning can be prevented with proper installation and use of home and workplace heating systems, especially those using gas, adequate ventilation, and routine maintenance. CO levels in exhaust gases can be reduced with regular maintenance and use of catalytic converters [12, 8]. Finally, although CO sensors do not register low levels of CO, they are still recommended for capacity to provide warning.

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