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CARBON MONOXIDE POISONING: LITERATURE REVIEW

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ABSTRACT

Carbon monoxide (CO) is known as a colorless, odorless, tasteless, and non irritating gas. CO produced from burning gasoline, wood, charcoal, propane, or other fuels. CO competes with oxygen to bind with Hb, forming COHb and leads to shifting the oxyhemoglobin dissociation curve to the left, reducing oxygen-carrying capacity, and oxygen release into the peripheral tissue. Tissue hypoxia due to CO induces vascular permeability and increased interstitial fluid accumulation with decreased circulating blood volume affecting multiple organs. Three clinical sequences consisted of symptoms consistent with CO poisoning, recent history of CO exposure, and elevated HbCO levels should be present in diagnosing CO poisoning. The current mainstay of CO poisoning treatment is high flow, normobaric (NBO) oxygen therapy administered as soon as possible.

Keywords: carbon monoxide, poisoning, intoxication, inhalation

ABSTRAK

Karbon monoksida (CO) adalah gas yang tidak berwarna, tidak berbau, tidak memiliki rasa, dan tidak menyebabkan iritasi. Gas CO dihasilkan dari pembakaran bensin, kayu, arang, propana, atau bahan bakar lainnya. Gas CO bersaing dengan oksigen untuk berikatan dengan Hb, membentuk COHb dan menggeser kurva disosiasi oksihemoglobin ke arah kiri, mengurangi kapasitas Hb membawa oksigen, dan mengurangi pelepasan oksigen ke jaringan perifer. Hipoksia jaringan akibat gas CO menginduksi permeabilitas vaskular dan meningkatkan akumulasi cairan interstisial yang menyebabkan penurunan sirkulasi darah dan pada akhirnya memengaruhi banyak organ. Tiga gejala klinis berupa gejala keracunan CO, riwayat pajanan CO, dan peningkatan kadar HbCO diperlukan dalam mendiagnosis keracunan CO. Pengobatan utama keracunan CO saat ini adalah terapi oksigen normobarik aliran tinggi yang diberikan sesegera mungkin.

Kata kunci: karbon monoksida, keracunan, intoksikasi

INTRODUCTION

Poisoning carbon monoxide (CO) is one of the most common causes of death. CO is a colorless, odorless, tasteless, and non irritating gas. The worldwide incidence of CO poisoning has remained stable during the last 25 years. It is estimated that there are about 137 cases and 4.6 deaths per million (Mattiuzzi C and Lippi G, 2020). CO can be produced endogenously from the human metabolism of hemoglobin but it is produced in low concentration. Carbon monoxide (CO) produced from burning gasoline, wood, charcoal, propane, or other fuels. In everyday life, this gas is contained in car fumes, motorbikes, stoves, cigarette smoke, lanterns, thinners, and other solvents (Gozubuyuk AA et al., 2017).

The inhaled carbon monoxide is rapidly absorbed. CO is distributed throughout the body by binding to heme protein. In the blood, CO binds to erythrocytes to form the COHb complex, whereas in muscle most of it binds to myoglobin to form COMb complex (US Department of Health and Human Services, 2012). The affinity of CO for hemoglobin (Hb) is 230 to 270 times greater than oxygen. The formation of COHb in blood depends on a wide variety of factors, including the concentration of inspired CO, duration of CO exposure, pulmonary ventilation, exercise and health status (Kinoshita et al., 2020). In the air in a standard room (21% O_2), the half-life of CO is 320 minutes. In 100% O_2, the half-life of CO is less than 90 minutes. With hyperbaric oxygen at a pressure of 3 ATA (atmospheres absolute), the half-life of CO is decreased to 23 minutes (Hanley ME and Patel PH, 2021).

Pathogenesis

CO is non-irritating gas present in the environment if at low concentration and has a similar molecular weight to air (Gozubuyuk AA et al., 2017; Eichhorn L, Thudium M, and Jüttner B, 2018). CO has a high affinity to binds ferrous heme-containing proteins such as hemoglobin (90%) in blood and rarely to myoglobin and Cytochrome C Oxidase in tissue (10%) (Eichhorn L, Thudium M, and Jüttner B, 2018). CO competes with oxygen to binding with Hb, forming COHb and leads shifting to the left of the oxyhemoglobin dissociation curve, reduce oxygen-carrying capacity, and oxygen release into the peripheral tissue (Eichhorn L, Thudium M, and Jüttner B, 2018; Rose JJ et al., 2017). However, the COHb bond is reversible (Kinoshita et al., 2020).

COHb levels are considered abnormal and may produce symptoms if COHb level ≥2% in nonsmokers and ≥10 in smokers (Rose JJ et al., 2017). Since elimination times in tissue and blood differ, tissue injury can also develop with a delay (Eichhorn L, Thudium M, and Jüttner B, 2018). The toxic effect of CO is caused by CO inhibition on oxygen delivery that leads to tissue hypoxia and binding to cellular heme-containing proteins such as myoglobin in the myocardium and skeletal muscle, causing dysfunctional tissue oxygen transport (Kinoshita et al., 2020; Rose JJ et al., 2017). Tissue hypoxia due to CO induces vascular permeability and increased interstitial fluid accumulation with decreased circulating blood volume affecting multiple organs. It includes brain edema with neurological symptoms and disorders of consciousness, pulmonary edema with respiratory failure, and renal failure.

In the myocardium, COHb causes cardiac dysfunction and inhibits enzymes such as Cytochrome C Oxidase. CO poisoning leads to myocardial cell apoptosis and produces intracellular oxidative stress. Erythropoietin reduces the dysfunction of the myocardium and brain by suppressing apoptosis through other pathways (Kinoshita et al., 2020). In mitochondria, CO makes ischemic and anoxic brain injury leading to cognitive deficits by binds the ferrous heme a3 in the active site of COX. COX inhibits, while oxidative phosphorylation slows down and decreasing ATP production in the brain and heart.

CO can lead to platelet activation and react with superoxide to inhibit mitochondrial function and increase platelet activation (Rose JJ et al., 2017). Activated platelets stimulate neutrophils' degranulation and release myeloperoxidase (MPO). It makes amplifying the inflammatory effects and generating reactive oxygen species (ROS) by xanthine oxidase ((Eichhorn L, Thudium M, and Jüttner B, 2018; Rose JJ et al., 2017). MPO and ROS will catalyze lipid peroxidation (Rose JJ et al., 2017). Since elimination times in tissue and blood differ, tissue injury can also develop with a delay (Eichhorn L, Thudium M, and Jüttner B, 2018).

Clinical Manifestation

It is impossible to understand the manifestations without referring to the pathophysiology behind the clinical findings. Byard states that the clinical manifestations correlate linearly with the amount of carboxyhemoglobin in the blood (Byard RW, 2019). The symptoms are shown in the table below reportedly reflect the CO-Hb level.

Table 1. Levels of CarboxyHemoglobin (Byard RW, 2019)

COHb (%)	Clinical Symptom
< 1	Normal range (due to endogenous production)
< 10	Smoker's blood (no symptoms)
10-20	Headache, fatigue, ear ringing
20-30	Headache, weakness, nausea, vomiting
30-40	Severe headache, dizziness, nausea, vomiting
40-50	Syncope, confusion, increased respiration and heart rate
50-60	Coma, convulsions, depressed respiration
60-70	Coma, convulsions, cardiopulmonary depression, often fatal
70 <	Respiratory failure, death

Contradictory to the statement before, Kinoshita et al. stated that the clinical symptoms of acute CO poisoning and severity do not always correlate with CO-Hb concentrations. This may be caused by concentration of inspired CO and exposure time, oxygenation following rescue and its concentration, and time elapsed between termination of CO exposure and blood sampling (Kinoshita et al., 2020).

Roderique et al. concluded that the correlation between clinical manifestations and plasma CO-Hb concentrations is not linear due to carbon monoxide's extra hemoglobin mechanism. This mechanism leads to various manifestations comprising many organ systems, mainly the nervous system, heart, and blood vessels. All of which can be seen in Fig. 1.

Not only do the manifestations differ inconsistently among different carboxyhemoglobin plasma levels, they also vary among individuals due to genetic and epigenetic variations coding the ion channels, producing various degree of susceptibility upon carbon monoxide (Rodrique JD, Josef CS, Feldman MJ, and Spiess BD, 2015).

Kinoshita et al. also stated that motor function is depressed before impairment of consciousness in CO poisoning cases. Thus victims may notice CO poisoning and try to improve the room ventilation but cannot move at all (Kinoshita et al., 2020).

Eichhorn et al. state the difficulty of detecting chronic poisoning with mild symptoms since the symptoms resemble influenza. In the long term, neurological injuries will manifest without the loss of consciousness, unlike other hypoxia mechanisms, among which are Parkinson's-like symptoms, akinetic-mutism, and persistent deficits in executive function, such as dementia, concentration deficits, or behavior abnormality. These constellations of neurological symptoms are collectively referred to as delayed neurological sequelae (DNS) (Eichhorn L, Thudium M, and Jüttner B, 2018; Rodrique JD, Josef CS, Feldman MJ, and Spiess BD, 2015).

The severity of initial intoxication did not necessarily correspond with the development of the neurological injury's manifestation. Eichhorn's study has observed that there are changes in subcortical structures and the pallidum, as well as hippocampal atrophy. The long-term damage can manifest, ranging from days to weeks after initial intoxication (Eichhorn L, Thudium M, and Jüttner B, 2018).

Veiraiah et al. reported that the neuropsychiatric features could appear up to 40 days after acute exposure. These include memory impairment, disorientation, apathy, mutism, irritability, inability to concentrate, personality change, emotional lability, neuropathy, incontinence, chorea, apraxia, psychosis, dementia, and parkinsonism (Veiraiah A, 2020).

The mechanism responsible for the neuropsychiatric findings is white matter demyelination, which is primarily caused by reactive oxygen species (ROS) produced in CO poisoning. ROS effects are widespread and include DNA/RNA damage, lipid peroxidation on myelin sheaths, protein oxidation/nitrosylation, programmed cell death, and immune system activation.

CO effect on the cardiovascular system manifests as a shock that is resistant to catecholamines. This is due to the increased production and release of nitric oxide (NO) – a potent vasodilating agent – into the circulation, leading to profound hypotension. This mechanism is believed to be the culprit of permanent significant neurological damage along with ROS and

hypoxia because hypoxemic hypoxia alone, explained by the classic HbCO theory, cannot explain such extent of neurological injury CO poisoning has caused (Rodrique JD, Josef CS, Feldman MJ, and Spiess BD, 2015).

CO also causes cardiac dysfunction by affecting the ion channels responsible for automaticity and cardiac conduction, leading to decreased heart rate (bradycardia), reduced contractility, vasodilation, and disrupted AV node conduction. One can also find tachycardia, which is contradictory to the mechanism previously presented (Wesam A, Elslam AE, and Amin DM, 2015). This can be explained by the large oxygenated hemoglobin functional reserve in humans. This adaptive mechanism won't be exhausted until HbCO levels exceeded 80%.

L-type Ca^{2+} channel in cardiac myocytes inhibited by CO can also be found in the pancreas, which reduces insulin secretion, subsequently causing hyperglycemia. These toxidromes are similar to calcium-channel blocker overdose, such as verapamil (Rodrique JD, Josef CS, Feldman MJ, and Spiess BD, 2015). Conduction blockade leads to arrhythmia, which can lead to death (Rodrique JD, Josef CS, Feldman MJ, and Spiess BD, 2015; Lee FY, Chen WK, Lin CL, and Kao CH, 2015)

CO also inhibits the epithelial sodium channel (ENaC) that can be found in pulmonary type II alveolar cells and the kidney. ENaC plays a role in sodium and subsequent water reabsorption from alveolar space and natriuresis in the kidneys. Dysfunction of ENaC causes accumulation of fluid in alveolar space, resulting in pulmonary edema (Rodrique JD, Josef CS, Feldman MJ, and Spiess BD, 2015).

Aguiar et al. reported that in CO poisoning, coma blisters or coma bullae in comatose patients are observed. Nevertheless, as CO deaths are relatively rapid, such blisters are frequently absent (Dinis-Oliveira, Aguiar M, and Magalhães T, 2019).

Autopsy findings reported by Kinoshita et al. that the cherry-red coloration of the skin is the most characteristic appearance of the body surface is in CO poisoning, which is usually observed when the CO-Hb concentrations exceed 30%. Autopsy reveals that the blood, organs, and muscles also show the cherry-red coloring caused by CO-Hb and carboxymyoglobin formation (Kinoshita et al., 2020; Chandravanshi LP and Pal M, 2018).

This characteristic skin and mucus membrane discoloration can also be found in living poisoned individuals (Chandravanshi LP and Pal M, 2018). In addition to that, pulmonary edema and generalized organ congestion are also observed. In the cases of prolonged periods of CO poisoning, necrosis of the globus pallidum is observed. The underlying mechanisms are thought to involve hypoxic brain damage and apoptosis (Kinoshita et al., 2020).

Characteristics associated with high short-term mortality are pH values <7.20, fire as the source of CO, loss of consciousness, high HbCO level, and need for endotracheal intubation during HBO_2 therapy.[7]

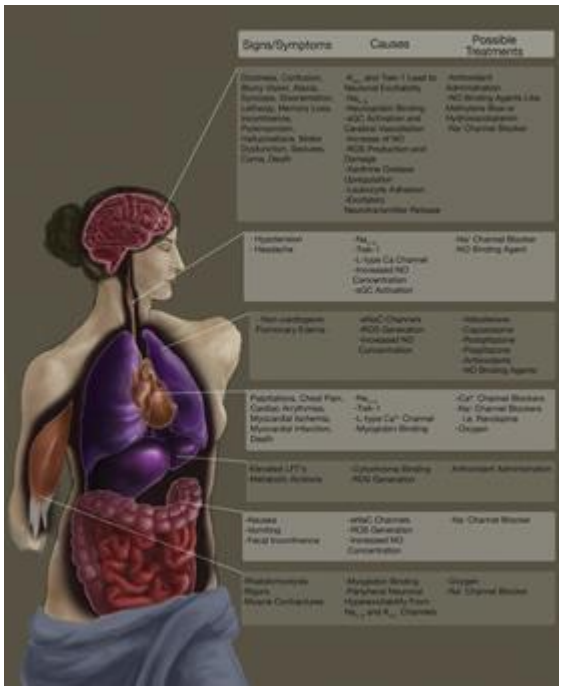

Fig.1. CO poisoning effects throughout the body (Rodrique JD, Josef CS, Feldman MJ, and Spiess BD, 2015).

DIAGNOSIS

Ideally, the clinical triad of (1) symptoms consistent with CO poisoning; (2) history of recent CO exposure; and (3) elevated HbCO levels; must be present in diagnosing CO poisoning. First criterion has been discussed in the previous section. The second criterion might be hard to obtain. There are some cases in which the risk of CO poisoning is chronic and low that the assessor underestimates it or doesn't aware of it. Potential CO sources include fire, engine exhaust (car, trucks), stoves, grills, lanterns, generators, and faulty furnaces (Rose JJ et al., 2017). CO detector is not common in Indonesia, but increased ambient CO from this device may direct clinician's suspicion of CO poisoning.

Hanley and Patel state that it is important to note that standard peripheral pulse oximeter devices cannot differentiate HbCO from oxyhemoglobin, and hence oxygen saturation (SpO_2) will not show any abnormalities. An arterial blood gas sample with a CO-oximetry analysis is the most useful initial step that will report the carboxyhemoglobin level (Hanley ME and Patel PH, 2021; Lee FY, Chen WK, Lin CL, and Kao CH, 2015).

Venous blood may also be used to measure the level of carboxyhemoglobin (Lee FY, Chen WK, Lin CL, and Kao CH, 2015). This widely accepted evidence can be traced back to two old studies, one was an observational study comparing arterial and venous carboxyhemoglobin in patients with suspected CO poisoning, and the other was an experimental study on piglets. Both of the studies concluded that venous HbCO concentrations predict arterial HbCO with a high degree of accuracy and are correlated at low, moderate, and high CO exposure concentrations (Touger M, Gallagher EJ, and Tyrell J, 1995; Lopez DM, Weingarten-Arams JS, Singer LP, dan

Conway JR EE, 2000). Spectrophotometer can also be used on the blood sample to measure HbCO level.

Other assessments such as a complete blood count, electrolytes, BUN, creatinine levels, and baseline troponin should be assessed. ECG should be done to seek any signs of ischemia because new ischemia on ECG indicates severe CO poisoning (Hanley ME and Patel PH, 2021). Supporting myocardial ischemia findings in ECG, cardiac biomarker – CK-MB and Troponin I – are high (Wesam A, Elslam AE, and Amin DM, 2015). Besides ischemic findings, QT prolongation, AV blockades, and other types of arrhythmia are also indicative of CO poisoning (Rodrique JD, Josef CS, Feldman MJ, and Spiess BD, 2015).

Kinoshita et al. state that spectrophotometric methods, gas chromatography, detection tubes, and oximetry are employed as a test for CO. The spectrophotometric method is the most widely used because of its simplicity. Additional considerations such as methemoglobin level (MetHb) in cases of automobile exhaust gas inhalation, as well as cyanide and MetHB level in cases of fire, should be measured (Kinoshita et al., 2020).

A retrospective-cross-sectional study by Doğruyol et al. states that it is found helpful to assess plasma lactate levels in the emergency department, considering that the poisoning mechanism is tissue hypoxia. This study found that the plasma lactate level has a significant correlation with HbCO. Plasma lactate level 3 mmol/L believed that it could be used as a cut-off value for severe exposure (Doğruyol S, Akbaş İ, and Tekin E, 2019). Other studies concluded that plasma lactate level does not rise appreciably until shortly before death when HbCO levels had already exceeded 80%. This evidence suggests that increased serum lactate is not reliable as screening (Lopez DM, Weingarten-Arams JS, Singer LP, dan Conway JR EE, 2000).

Head imaging such as CT scan or MRI is not indicated in CO poisoning but is frequently ordered because the common presenting symptom of CO poisoning is altered mentation. The most common MRI findings are generally white matter hyperintensities (WMHs) and hippocampal atrophy (Weaver LK, Orrison WW, Deru K, and McIntosh J, 2015). Other studies concluded bilateral globi pallidi with restricted diffusion may be a characteristic MRI feature in patients with acute CO poisoning, but this finding doesn't correlate well with carboxyhemoglobin levels (Kim DM et al., 2017).

MANAGEMENT

The current mainstay of CO poisoning treatment is high flow, normobaric (NBO) oxygen therapy administered as soon as possible (Rose JJ et al., 2017; Rodrique JD, Josef CS, Feldman MJ, and Spiess BD, 2015). Oxygen therapy can be performed by reservoir balloon mask (15 L/min O_2), non-invasive continuous positive airway pressure (CPAP) ventilation with 100% FiO_2, or endotracheal intubation (Eichhorn L, Thudium M, and Jüttner B, 2018). Selection of oxygen device is based on the clinical status of the patients. Oxygen is administered until the clinical symptoms disappear, usually about 4-5 hours (Centers for Disease Control and Prevention, 2020). NBO reduces the average half-life of HbCO from 320 minutes in patients breathing normal room

air to 71 minutes in patients breathing 100% oxygen via a nonrebreathing mask (Rodrique JD, Josef CS, Feldman MJ, and Spiess BD, 2015).

The half-life can be further reduced by increasing the pressure. This other option of oxygen therapy is hyperbaric therapy (HBO). The evidence to recommend HBO is still insufficient. The pressure administered in HBO is more than 1 atm, usually ranging between 2.5 to 3 atm (Eichhorn L, Thudium M, and Jüttner B, 2018; Rodrique JD, Josef CS, Feldman MJ, and Spiess BD, 2015).

HBO differs from NBO fundamentally in two significant ways: (1) HBO further reduces the half-time of HbCO, and (2) HBO increases the partial pressure of oxygen (PaO_2). Reduction of average half-life to 21 minutes can be obtained by administering 1.5 atm of 100% oxygen (Rodrique JD, Josef CS, Feldman MJ, and Spiess BD, 2015). Theoretically, HBO elevates PaO_2 and tissue oxygen partial pressure, therefore, enhances the elimination of CO. In practice, however, because the manifestations of CO poisoning are not solely due to reduction of oxygen delivery secondary to elevated HbCO, the patient outcomes don't correlate well with the speed of HbCO elimination and partial pressure of oxygen increase.

Additional supporting evidence to suggest HBO as the primary therapy for CO poisoning is a reversal effect on inflammation and mitochondrial dysfunction induced by CO poisoning. HBO increases adenosine triphosphate (ATP) production, which in turn reduces oxidative stress and inflammation (Casillas S et al., 2019). Contradictory to the explanation before, oxygen therapy at all pressures has the potential for a significant free radical generation (Rodrique JD, Josef CS, Feldman MJ, and Spiess BD, 2015). This is especially true for HBO, in which it improves cellular respiration inhibited by CO but increases H_2O_2 production (Jang DH et al., 2018; Friedman P, Guo XM, Stiller RJ, and Laifer SA, 2015).

American College of Emergency Physicians acknowledges HBO as a therapeutic option for CO poisoning but does not mandate HBO's use. HBO may be considered only in acute severe CO poisoning, which is cases with one or more of the following symptoms: loss of consciousness, ischemic cardiac changes, neurological deficits, significant metabolic acidosis, COHb more than 25%, pregnant patients, or elderly (Eichhorn L, Thudium M, and Jüttner B, 2018; Rodrique JD, Josef CS, Feldman MJ, and Spiess BD, 2015; Centers for Disease Control and Prevention, 2020; Casillas S et al., 2019; Idil H and Unek O, 2019). The downside of HBO includes barotrauma, hypoxic seizures due to high intake of oxygen in a short period, pulmonary edema, and is not readily accessible, particularly in developing countries (Rodrique JD, Josef CS, Feldman MJ, and Spiess BD, 2015; Casillas S et al., 2019).

Instead of HBO, NBO via non-invasive CPAP ventilation might be a better option since it provides tissue oxygenation rapidly and is more available in primary healthcare facilities. Non-invasive CPAP ventilation is more superior to reservoir balloon masks for it increases FiO_2 to 100%. CPAP also increases the diffusion area and gas exchange of the lung by preventing alveolar collapse (Martin NA and Garcia GR, 2016).

Another proposed therapy for CO poisoning is ozone therapy (O_3), which counteracts CO-induced ROS production by stimulating the systems' enzymatic antioxidants. Through its highly reactive radical characteristic, ozone immediately reacts with antioxidants, carbohydrates,

proteins, PUFA, etc., acting as pro-drug generating chemical messengers that will accelerate the transfer of electrons and the overall metabolism. The therapeutic window is small but ensures a small and accurate oxidative stress capable of causing medical efficacy, ranging from 10 to 80 µg/mL O_3 per mL of blood (Tanaka T et al., 2016).

Another proposed treatment modality for acute CO poisoning is light irradiation with a certain amount of luminance and distance as close as possible to the light source. This measure dissociates CO from Hb, i.e., reducing the half-life of HbCO, with minimum effect on HbO_2 (Zazzeron L et al., 2019). Phototherapy studies in CO-poisoned rats also yielded encouraging results, which extracorporeal removal of CO with phototherapy double the rate of CO elimination (Rose JJ, Xu Qz, Wang L, and Gladwin MT, 2015).

In vitro and experimental studies in animals have been done with promising results, but in vivo research in humans has yet been done.[27] The delivery of luminance is food for thought. One proposed method is extracorporeal photodynamic blood illumination, in which the blood is removed externally to be exposed to an illuminator and reperfused back into the patient (Li Qin et al., 2016).

Alternative treatments are free radical scavengers such as edaravone, antioxidants, and ion-channel-modifying agents to counteract the channel-blocking effects of CO (Rodrique JD, Josef CS, Feldman MJ, and Spiess BD, 2015; Li Qin et al., 2016; Mori K et al., 2015).

CONCLUSION

Carbon monoxide is a dangerous gas because it can damage many organs. The symptoms of carbon monoxide poisoning can be chronic and difficult to detect, even with oxygen saturation. The most useful examination in assessing carboxyhemoglobin levels is with CO-oximetry. Treatment of carbon monoxide poisoning needs to be done as soon as possible in order to reduce the level of carbon dioxide quickly from the blood.

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