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REVIEW ARTICLE

Carbon Monoxide Intoxication – Review

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Summary

Carbon monoxide (CO), is a toxic gas produced by incomplete combustion of carbon containing materials such as kerosene, gasoline, propane and coal. As it's a colourless, odorless, tasteless and non-irritating gas, CO is described as the "silent killer".

CO, binds to the iron atoms in hemoglobin, with an affinity 200-250 times that of oxygen, and impairs oxygen carrying capacity of the blood. Hence, CO toxicity is a situation characterized by impairment of oxygen transportation and consumption. It has been reported that 30% of such cases are not diagnosed since the signs and symptoms in CO intoxication. Definitive diagnosis of CO intoxication is established by measuring the COHb concentration in arterial or venous blood.

Elimination half life of COHb and partial oxygen pressure produced by inspired oxygen concentration is closely related. High levels of inspired oxygen fractions both accelerate CO removal and improve oxygenation. Hyperbaric oxygen (HBO) treatment is first discussed in 1890's and was initially used in 1960's. Although, acceleration of removal of the CO from hemoglobin was aimed initially, other effects were recognized in time. When HBO treatment is not possible, high flow 100% oxygen is applied via tight-fitting face mask. for 6-12 hours. Although, the dominance of f HBO to normobaric oxygen theraphy has been supported by several studies, more randomized clinical trials are needed.

In general, most of the CO intoxications are nonfatal. Cases with mild symptoms and those that do not show any neurological symptoms can be discharged from hospital after 4-6 hours of treatment. Despite the therapy, it is still impossible to predict long term results of CO intoxication.

Key Words: *Carbon monoxide, Intoxication*

Karbon Monoksit Zehirlenmesi - Derleme

Özet

Karbon monoksit (CO), benzin, propan, gaz yağı, kömür gibi karbon içeren materyallerin yanması sırasında üretilen toksik bir gazdır. CO, renksiz, kokusuz, tatsız ve irritan olmayan özellikleri nedeniyle "sessiz öldürücü" olarak da tanımlanmıştır.

CO, hemoglobindeki Fe^{+2} atomuna, oksijene göre 200–250 kat daha fazla oranda bağlanarak kanın oksijen taşıma kapasitesini azaltmaktadır. Bu nedenle CO toksisitesi, temel olarak oksijen transportunun ve kullanımının bozulmasıyla karakterize bir durumdur. CO toksisitesinin bulgu ve semptomları non-spesifik ve değişken olması nedeniyle yaklaşık %30 zehirlenme vakasının tanı almadığı rapor edilmiştir. CO toksisitesinin kesin tanısı arter veya venöz kandaki COHb konsantrasyonunun ölçümüyle konmaktadır.

COHb'nin eliminasyon yarı ömrü ile FiO_2 tarafından oluşturulan PaO_2 arasında yakın bir ilişki gösterilmiştir. Yüksek FiO_2 düzeyleri, CO eliminasyonunu hızlandırmanın yanı sıra oksijenizasyonu da düzeltmektedir. Hiperbarik oksijen (HBO) tedavisi ilk kez 1890'larda tartışılmış ve ilk kez 1960'larda kullanılmıştır. İlk kullanımında CO'in hemoglobinden ayrılmasını hızlandırmak amaçlansa da, diğer etkileri zamanla anlaşılmıştır. HBO tedavisinin mümkün olmadığı hastalara 6-12 saat süreyle yüze sıkı oturan bir maske ile yüksek akımla %100 oksijen uygulanır. HBO tedavisinin, normobarik oksijen tedavisine üstünlüğü bazı çalışmalarla desteklense de bu konuda daha çok randomize klinik deneye ihtiyaç vardır.

Genel olarak, CO ile zehirlenme vakalarının çoğu non-fataldir. CO toksisitesi gelişen hastalar orta dereceli semptomlardan başka semptoma sahip değilse, nörolojik bulgular normalse ve herhangi bir medikal tedaviye gereksinim duyulmuyor ise 4–6 saat sonra taburcu edilebilirler. Fakat tedaviye rağmen CO zehirlenmesinin uzun dönem sonuçlarını ön görmek hala mümkün değildir.

Anahtar Kelimeler: *Karbon monoksit, Zehirlenme*

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Carbon monoxide (CO) is a toxic gas with non-polar molecular structure produced by incomplete combustion of carbon containing materials such as kerosene, gasoline, propane and coal. It has been defined as the "silent killer" due to its colorless, odorless, tasteless and non-irritating structure. It diffuses itself as low-density structures in closed areas and can exist even when there is no fire or smoke in the environment (1).

CO intoxication is seasonal and shows regional variations. More than 80% of deaths due to CO intoxication are because of the sources used for indoor heating. In the United States, 14.000 to 40.000 acute CO intoxication cases due to fire and other sources were detected per year. During 1999–2003, 439 deaths per year have been reported on avarage. CO intoxication in this regard, is the third in the list of accidental deaths in the US (1, 2). 5000 to 8000 patients per year apply to the hospitals in France due to CO intoxication while this number in Italy was 6000 per year during 1993-1994. The number of deaths due to CO intoxication within the same period was more than 300 (3). Besides, due to the fact that 1/3 of CO intoxications are not diagnosed, the importance of the subject enhances (4).

Pathophysiology in Carbon Monoxide Intoxication;

CO enters the body via lungs and reversibly binds to the oxygen carrying component hemoglobin. It decreases the oxygen carrying capacity of hemoglobin by binding the Fe^{+2} atom of hemoglobin 200–250 times more readily. Therefore, CO toxicity is a situation basically characterized by impaired oxygen transport and usage. Increased affinity of CO to oxygen and the decrease in the oxygen binding capacity of hemoglobin is known as the "Haldane Effect" (5). This situation leads to tissue hypoxia which is characterized by decreased oxygen transport and impaired oxygen supply as a result of a leftward shift in the oxyhemoglobin dissociation curve. Decrease in the ATP production due to binding of CO to the intracellular proteins such as "myoglobin" and "cytochrome-C oxidase", mitochondrial function disorder leading oxidative phosphorylation impair and tissue toxicity leading cell death, which is characterized by lactic acidosis develop simultaneously (1). In this regard, in cases which develop CO toxicity despite hyperbaric oxygen (HBO) therapy, it is the effects on mitochondria which determine the lifetime (1, 6).

Affinity of CO to myoglobin is approximately 30–60 times more than that of the oxygen. When it binds to myoglobin, oxygen supply to mitochondria in tissues like heart muscle impairs. Impaired oxygen supply in turn breaks down oxidative phosphorilation and energy production. This situation manifests itself as rabdomyolisis in the striated muscles, dysfunction and arrhythmia in the heart (7, 8, 9).

Cytochrome-C oxidase is a terminal enzyme of electron transport chain. As CO binds to cytochrome oxidase, oxygen usage and cellular respiration impair in all tissues including the brain (10). Energy production and mitochondrial function recover after the decrease in the carboxi-hemoglobin (COHb) levels. However, happily, the amount of CO to inhibit all cytochrome is thousand times of the lethal dose. Thus, this mechanism does not play a crucial role in the patient's clinic situation (11).

In acute CO intoxication, neuronal necrosis or apoptotic cell death may develop (12). This process is probably responsible for some of the initial neurological abnormalities (13). Neuropathological changes in acute CO intoxication have been explained by four mechanisms: ischemic nerve damage due to hypoxia induced by CO, direct peripheral nerve damage due to high level of CO, existence of petechial hemorrhage in peripheral nerves as in other organs, development of venous obstruction due to local edema and circulation impair (14).

CO causes "nitric oxide (NO) " release from endothelial cells and thrombocytes and results in the proinflammatory response which develops due to the increase in the formation of nitric oxide derivative oxidants such as peroxynitrite that leads to endothelial damage and leukocyte sequestration. This mechanism has been detected to be related with the production of neutrophil originated reactive nitric oxide derivatives (RNS) like peroxynitrite which is released from thrombocytes and reacts with NO (15).

When NO synthesis is stimulated in thrombocytes in the presence of CO, "heterotypic" thrombocyte-neutrophil aggregation is also stimulated. Thus, thrombocyte adhesion molecules are activated by direct binding of peroxynitrites. When physical connection is established between thrombocytes and neutrophils, significant neutrophil-derived RNS increase develops which contributes "neutrophil degranulation" (16). Concurrently, it has been reported in CO toxicity that "myeloperoxidase (MPO) " concentrationincreases in the brain and is stored along the vascular line and leads to vascular oxidative stress due to colonization with nitrotyrosine.Regarding this pathology, by catalyzing the reaction that nitrite and hydrogen peroxide arise from nitrogen dioxide, MPO stimulates the nitrite, local tyrosine residuals, formation and the expression of endothelial adhesion molecules which causes lipid peroxidation (17). Accumulation of MPO and nitrotyrosine along the subendothelial line was detected in human tissues in various inflammatory pathologies (18). Activation of xanthine oxidase causes lipid peroxidation in the brain which is responsible for the formation of oxidative radicals, oxidative damage and late neurological sequels (19-26). As a result of the interaction between lipid peroxidation products and myelin basic protein (MBP), the three-dimensional structural change in MBP has been shown (27).

Overall, it has been emphasized that the interaction between thrombocytes and neutrophils and the neutrophil degranulation is the main component of neurotoxicity due to CO. CO intoxicity causes thrombocyte and neutrophil activation which in turn causes free radical formation by increasing lipid peroxidation in brain and other tissues via immunological mechanism. Also, it causes late degeneration of the white matter in the nervous system by development of cellular edema and cell death due to degeneration of unsaturated fatty acids in certain areas (17, 18, 27).

In the view of such mechanisms, as it is valid in all other toxicities, the damage depends on the CO concentration, exposure interval and the health situation of the patient.

Clinical Picture in Carbon Monoxide Intoxication; Due to nonspecific and variable findings and symptoms of CO toxicity, approximately 30% of toxicity cases have been reported undiagnosed. In case of low or extremely high blood CO concentration levels, blood levels and the severity of clinical findings correlate. Acute toxicity may cause functional disorders of multiple organ systems particularly with the involvement of central nervous and cardiovascular systems. Neuropsychiatric sequels, not clearly identified but similar to euphoria, were reported in a small group of patients. Euphoria tends to be together with forms of acute psychosis and its differential diagnosis should be confirmed in early CO intoxication (28). When the blood COHb is under 15–20% level, there are non-specific symptoms like dizziness, nausea, vomiting, diarrhea, feebleness and weakness. It has been accepted that the reason for the headache in CO toxicity is an effect causing relaxation of the vascular smooth muscles which in turn leads to vasodilatation of extracranial arteries (29). Because the symptoms at this stage may also imply a viral pathology, CO toxicity may be overlooked. However, cases with 20–40% blood COHb levels present symptoms like nausea, vomiting, confusion with subjective sophisticated thoughts, disorientation and visual impairment while cases with 40–60% blood COHb levels present neurological (agitation, irritability, ataxia, hallucination, coma), cardiovascular (hypotension, arrhythmia, ischemia, shock) and pulmonary (tachypnea, edema, respiratory failure) malfunctions. Attacks, loss of consciousness and death had been observed in cases with higher than 60% blood COHb levels (30). Isolated attacks were also reported in pediatric patients (31, 32). It has been stated that if there are symptoms which can be shown with simple neurological tests, defects in the cerebral cortical function may be overlooked in severe CO intoxication (33). Neuropathic changes due to CO intoxication are characterized by the hemorrhagic necrosis of globus pallidus and demyelination of cerebral white matter (34). In addition, in severe cases with elongated exposure, loss of consciousness and stupor develops after 48 hours and "retinal hemorrhage" accompanies (28).

Myocardial damage due to CO intoxication can be observed because of the toxic effect on the myocardial mitochondria and myocardial hypoperfusion. This clinical picture rapidly proceeds after CO exposure and may comprise several arrhythmias including ventricular extrasystole and fibrillation without tachycardia and myocardial damage (35). Diagnostic electrocardiographic changes and/or increase in cardiac indicators have been detected in 37% of the patients after mild and severe CO intoxication (36). Despite the high frequency of myocardial damage, mortality remains below 5%. When long term mortality follow ups of 230 CO intoxication cases were evaluated; myocardial damage was observed in 85 patients (37%) (troponin-I >0.7ng/mL, CK-MB >5 ng/mL, ECG changes) while no myocardial damage was found in 145 patients. In the follow ups of patients with myocardial damage, death was detected with a ratio of 38% in 7.6 years in average (37). Correlation was also reported between systemic hypotension and the level of the structural damage in the central nervous system (7, 38-42).

Among the non-lethal complications of CO toxicity, central nervous system dysfunction characterized by psychomotor weakness and neuropathy were observed. In the clinical picture of CO intoxication, there are "persistent" (simultaneous to toxicity) findings like hearing loss, memory loss, confusion, ataxia, attacks, enuresis and encopresis, labile emotional status, disorientation, hallucinations, parkinsonism, mutism, cortical blindness, psychosis and motor defects and "late" neurological findings which are seen on the 2^{nd}-40^{th} days after the recovery of acute intoxication. These findings may be reversible or not (4, 43-48). Although the incidence of late findings shows variability in different series (12-68%), it is reported as 11.8% in subgroups in which hospitalization was needed. In the same series, recovery of late findings in a year was observed in 75%. Incidence of late findings was found to be positively correlated with the duration of consciousness loss during the acute intoxication and the patient's age (13, 28, 49).

Peripheral neuropathy is almost always characterized by typical local edema in the lower extremity and the pathological findings of demyelination. Another example for peripheral neuropathy in CO toxicity is defined as the reversible and unilateral diaphragmatic paralysis (14).

Pregnant women who are exposed to CO toxicity are subject to a particularly difficult situation. CO slowly moves along placenta, thus the elimination from both the mother and fetus elongates approximately twofold. Hence, the fetus is more susceptible to CO toxicity and this may result in death, articular and vertebral anomalies and cerebral damage (50-52). Exposure in the early stages of pregnancy leads to anatomical malformations while functional and neurological disorders can be observed due to exposures at any stage (53-56).

Because of the fact that CO has direct toxic effects on skeletal muscles, it can cause rhabdomyolysis. Acute renal failure was also reported in severe rhabdomyolysis cases (57-59). Among the other reported findings in severe intoxication cases are the cutaneous blister formation and noncardiogenic pulmonary edema (60-63).

Diagnosis in Carbon Monoxide Intoxication;

The diagnosis of intoxication is based on the detection of CO exposure due to sources such as building fires, inappropriately set oil, wood or kerosene burners, coal- or gas fueled barbecue.

There is no difference between the arterial or venous blood COHb and the absolute the toxicity is diagnosed for certain by measuring the arterial or venous blood COHb concentration. If the patient has been breathing the air in the room for the last few hours, COHb concentration measurements are less useful. Concentrations over 2% in nonsmokers and 9% in smokers support CO exposure. However, it may not always show accurate correlation with the clinical situation although it is a practical marker. The determinative point for clinical picture is the duration of the exposure and the biological condition of the patient along with the CO concentration. CO is also endogenously produced as a product of hem metabolism. Thus, in patients with elevated COHb levels, the fact that it may develop due to hemolysis in

hemolytic or sickle cell anemia should be should not be overlooked. COHb concentrations in heparinized blood samples stay stable during 4 weeks in cold or in room temperature and can be transferred to another center for the determination of COHb concentration. In case of fetal Hb existence, inadvertently increased levels of COHb can be observed. Thus, false positive 7–8% COHb concentration levels have been reported for the first few weeks of infants. For the CO toxicity patients, the duration for which the patient is exposed the toxic environment is also important. Another approach is to document the expired CO by analyzing the respiratory tract air. These measurements may be difficult in uncooperative patients. It has been observed that 0–6 ppm of CO is found in the expired air of nonsmokers while it is over 70 ppm in smokers. CO measurement in ambient air is another alerter test and CO concentrations higher than 50 ppm should be cautionary (64).

Since myocardial damage development has been detected in 37% of patients intoxicated by CO. ECG and measurement of cardiac biomarkers in blood are essential in cases of serious CO intoxication. In patients intoxicated by CO with elevated cardiac enzymes and ECG changes, increased mortality rates have been found in the following few years, despite aggressive treatment. It has been observed that angina attacks increase in patients with chronic angina with a mild increase in the COHb levels, and it is possible to observe arrhythmias in patients with coronary artery disease when the level of COHb increases to 6%, and it was shown that in cases with severe CO toxicity ischemia can develop even if the patients have normal coronary arteries (37).

COHb has a bright red color. Classically, "cerise" color of blood cannot be observed in the patient because this can only be observed in concentrations over 40%. This can be masked by the simultaneous presence of hypoxia and cyanosis. In such cases, normal pulse oximeter (SpO_2) despite a decrease in the arterial oxygen saturation does not eliminate CO toxicity (65). SpO_2 provides a noninvasive measurement for the estimation of arterial hemoglobin saturation with oxygen. There are four typical types of hemoglobin in the adult blood as oxyhemoglobin (O_2Hb), reduced oxyhemoglobin (RHb), methemoglobin (MetHb) and carboxyhemoglobin (COHb). Arterial oxygen content decreases as the COHb increases. It has been reported in experimental animal studies that when COHb concentration is increased up to 50%, SpO_2 level is measured 94% as FiO_2 is 1.0. In such a case, the oxygen saturation measured by SpO_2 is slightly decreased, in proportion to the increase in COHb. This is because of the fact that with pulse oximetry, COHb and O_2Hb show similar characteristics in absorbing the waves of the light. Both absorbs red lightof wavelength 660nm while they do not absorb infrared light of 940nm. Thus, the measured SpO_2 actually reflects the sum of O_2Hb and COHb (66).Radiological findings of CO toxicity comprise ground-glass appearance in lungs, perihilar blur, peribronchial and perivascular fullness and interstitial edema (14). Globus pallidus infarct, hypodensity in the subcortical white matter, cerebral cortex lesions, cerebral edema, hippocampus lesions and lesions with gray-white matter differentiation loss are the findings central nervous system due to CO toxicity (67, 68). Existence of such radiological findings is the sign of cerebral infarct secondary to ischemia or hypoxia and has been related to poor prognosis.

Therapy in Carbon Monoxide Intoxication;

Even if there is no smoke inhalation accompanying distinct pulmonary damage in CO intoxication, FiO_2 should be continued at the highest possible concentration. A close relationship has been shown between the elimination half-life of COHb and the PaO_2 formation by FiO_2. High FiO_2 levels accelerate CO elimination along with the correction of oxygenation. Half-life of COHb is 240-320min. at room air while it is 40 to 80min. with 100% oxygen support and 20min. with 100% oxygen at 2.5-3 atm pressure (69-72).

HBO therapy was first discussed by Haldane in 1890's and was first used in 1960's (73). Initially, the aim was to accelerate the leave of CO to leave hemoglobin; its other effects were recognized in time. Having a COHb level of over 25% at any stage of the exposure, having neurological functional disorders including consciousness loss, ischemia, arrhythmias,

cardiac functional disorders such as ventricular failure and metabolic acidosis are among the required criteria to apply HBO (10, 47, 48, 74-83). Same criteria are used for the infants and the children as well (84). Empiric therapy with HBO was recommended in reports for pregnant women with CO concentrations of 15–20%(51, 80, 85). Furthermore, pregnant women may need longer oxygen therapy than non-expecting ones (86-90).

Although HBO therapy is widely used today, there are no standard regarding the therapy time or frequency (91). However, a session of HBO at 2.5-3 atm is applied to the patient who meet the criteria (74, 85). Additional sessions are evaluated considering the clinical findings and the elimination of the symptoms. For the patients who does not meet the criteria or application of HBO therapy is not possible, high flow of 100% oxygen is administered with a tight-fittingmask for 6-12 hours (7, 74, 92, 93).

Many authors emphasized the reliability of HBO therapy. Anxiety and barotrauma to middle ear and sinuses which are seen in 0–80% of the patients who have had HBO therapy are among the most common complications (79, 80, 82, 83). Seizures, oxygen toxicity, pulmonary edema and pulmonary bleeding, pneumothorax and air embolism are among the less often complications (91, 94, 95). The single absolute contraindication for HBO therapy is the untreated pneumothorax (85). Claustrophobia, otosclerosis or other middle ear diseases, intestinal obstruction, chronic obstructive lung disease with bulla formation or the need to certain procedures like aspiration, defibrillation, cardioversion and intubation are among the relative contraindications. It should be kept in mind that minutes are needed for safely decompression of the patient (96)

HBO decreases neutrophil adhesions to endothelium (97, 98) while the oxidative damage due to free radicals (29, 96, 97) and its effects on neurological sequels are a matter of debate (12, 25). With HBO therapy, both removal of CO from intracellular binding areas and increase in the ratios of elimination of CO from Hb is provided. This in turn provides a shortage in coma duration and a decrease in early mortality in the acute intoxication stage. Long term effects of HBO therapy in CO intoxication are various. During reoxygenation after hypoxia, HBO increases inflammation by increasing the amount of plasma reactive oxygen types (ROT) (99) and inhibits lipid peroxidation in brain. Furthermore, HBO decreases NO synthesis by inhibiting inducible nitric oxide synthase (iNOS) enzyme. Another effect of HBO is to increase the anti inflammatory effect by activating the hem-oxygenaz-1 (HO-1) enzyme (100).

In the meta-analysis of Juurlink (101) in 2005, 6 studies which compare the efficacy of normobaric oxygen therapy (NBO) and HBO therapy for CO intoxication were evaluated. Among those, two studies by Thom (16) and Weaver (102) showed that HBO therapy is more efficient than NBO therapy while the other 4 did not find significant differences between the two therapies. Although it was observed that HBO therapy is more efficient, no significant statistical difference was found. However, methodological and statistical differences were mentioned and it has been noted that there is the need for wider randomized studies

Prognosis in Carbon Monoxide Intoxication;

In general, most of the CO intoxication cases are non-fatal. Patients with CO toxicity can be discharged in 4 to 6 hours if there is no other symptoms than mild symptoms, if they have normal neurological findings and if they do not need any medical therapy. But, it is still impossible to foresee the long term results of CO intoxication despite therapy.

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