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Is Asymotomatic Low-Dose Carbonmonoxide Poisoning Harmless at Emergency Department Presentation?

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Abstract

Aim: Carbon monoxide (CO) poisoning is a common inhalation poisoning in emergency department (ED) admissions. In this study, we aimed to determine the negligible biochemical and electrocardiogram (ECG) pathological findings of this group of patients with CO poisoning and asymptomatic clinical cases with a CO level below 15% at first admission who are frequently discharged from the ED.

Materials and Methods: A total of 68 patients who were exposed to CO poisoning who did not have any clinical complaints or symptoms at the first examination and whose carboxyhemoglobin (COHb) level was between 5% and 15% were included in the study. The group with a COHb level of 5-10% was considered to have a very low level, whereas the group with a COHb level of 10-15% was considered to have a low level. Among the laboratory findings at the time of admission, the COHb level measured at the time of admission to the ED, troponin a cardiac marker, potential of hydrogen and lactate measurements, and white blood cell (WBC) and neutrophil levels were recorded. ECG data were recorded.

Results: With regard to COHb levels of low-dose and very low-dose CO poisoning, ECG parameters showed a significant difference, but not in heart rate (p=0.001) between the groups. Regression analysis was performed between ECG heart rate and COHb level, and the linear regression equation was found to be $y=2.38x+58.32$ ($r^2=0.68$).

Conclusion: It should be kept in mind that patients may sometimes present with low COHb levels at ED presentation. If patients have available ECGs, they should definitely be compared with their previous ECGs, and blood parameters, especially lactate, troponin, WBC, and neutrophil levels, should be evaluated. It should not be forgotten that tissue and organ damage can occur with low-dose poisoning.

Keywords: Carbon monoxide, electrocardiogram, emergency department, blood parameters, heart rate

Introduction

Carbon monoxide (CO) is an odorless, tasteless, colorless, and extremely toxic gas formed with the combustion of hydrocarbons (1).

CO reacts with hemoglobin in the blood, metalloproteins such as myoglobin in the tissues it reaches through the blood, and metalloenzymes such as cytochrome c oxidase, cytochrome P450, tryptophan oxygenase, and dopamine hydroxylase, causing tissue and organ damage (2,3).

Of the absorbed CO, 80% binds to hemoglobin in erythrocytes and form carboxyhemoglobin (COHb). Of it, 10-15% reacts with myoglobin in muscle cells. The affinity of myoglobin for CO is one-eighth that of hemoglobin. Cardiac muscle cells retain more CO than skeletal muscle cells (4).

Furthermore, CO causes lipid peroxidation in the brain (3). In the clinic, patients frequently encounter symptoms and signs of CO poisoning, especially in the central nervous and cardiovascular systems (3,4).

COHb levels of 5% and above in non-smokers and 10% and above in smokers are considered significant. In normal cases, a COHb level below 10% is considered very low-level poisoning (5). In low-level CO poisoning, asymptomatic patients, patients with mild non-specific symptoms, and patients with a CO level of 15% or below are considered low doses (6).

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Since there are no serious side effects of low-dose CO poisoning in the emergency department (ED), changes in the physiologic limits are ignored by physicians, and it is thought that there is no problem. However, we believe that this may affect the side effects and outcomes of low-dose CO poisoning at the cellular level and may cause serious cardiac problems in patients with comorbidities.

In this study, we aimed to determine the negligible biochemical and electrocardiogram (ECG) pathological findings of a group of patients with CO poisoning and asymptomatic clinical cases with a CO level below 15% at first admission who are frequently discharged from ED.

Materials and Methods

The study was initiated with the approval of the Niğde Ömer Halisdemir University Non-Invasive Clinical Research Ethics Committee (decision number: 2023/56, date: 24.08.2023). However, due to the retrospective study design, the requirement for informed consent was waived.

This study was conducted with strict adherence to the methods and recommendations of Worster et al. (7) for medical record review in emergency medicine research. Among patients who presented to Niğde Ömer Halisdemir Training and Research Hospital between 01.11.2021 and 30.06.2023, patients diagnosed with toxic effect of CO toxic effect of carbon monoxide (T58) ICD10 code were retrospectively screened through our hospital's automation system (Karmed). The patient data were created digitally (in the Microsoft Excel program) and added to the study data form. In this data form, demographic data included the gender of the patients, and among the information regarding CO exposure, whether the source of CO was from the stove/water heater/heater, fire/smoke, or exhaust gases was recorded. Patients' chronic diseases were recorded in the medical history section of the data form. The study investigated whether patients had chronic diseases, such as diabetes, coronary artery disease, hypertension, cerebrovascular diseases, congestive heart failure, or chronic obstructive pulmonary disease (COPD). All patients who were exposed to CO poisoning and brought by emergency ambulance teams, did not have any clinical complaints or symptoms at the first examination, and had a COHb level between 5% and 15% were included in the study. The group with a COHb level of 5-10% was considered very low, and the group with a COHb level of 10-15% was considered low. Among the laboratory findings at the time of admission, the COHb level measured at the time of admission to the ED, troponin a cardiac marker, [potential of hydrogen (pH) and lactate measurements, and white blood cell (WBC)] and neutrophil levels, which are among the blood gas parameters, were recorded.

The ECGs of patients during their admission to the ED were evaluated, and the QT interval, rate in beat/min, and PR interval were evaluated on the ECG and added to the digitally created study data form (in the Microsoft Excel program).

Inclusion Criteria

Non-pregnant patients over the age of 18 and under the age of 65 with a COHb level between 5-15% who presented to the adult ED of Niğde Ömer Halisdemir Training and Research Hospital between 01.11.2021 and 30.06.2023 and were evaluated using the T58 ICD10 diagnostic code were included in the study regardless of the source of CO poisoning in acute CO poisoning.

Exclusion Criteria

Patients whose data to be used in the study could not be accessed through our hospital's automation system in the retrospective screening, patients with T58 diagnosis code entry without measuring CO levels but whose CO levels were measured lower than 5% and higher than 15%, and patients whose file data could not be accessed or whose data were missing were excluded from the study.

Patients younger than 18 years and older than 65 years during the first admission were not included in the study.

Patients working in closed areas where they may be exposed to chronic CO were excluded from the study. Smokers were excluded from the study.

Pregnant women were excluded from the study. According to the information obtained from the anamnesis records upon admission to the ED, patients with agitation and anxiety were excluded from the study.

Statistical Analysis

Along with descriptive statistics, continuous data were expressed as mean ± standard deviation. Categorical variables were presented as frequency and percentage. χ^2 was used to test for significant differences in terms of CO levels between the study groups (study group 1:5-10% CO level and study group 2:10-15% CO level), and appropriate Statistical tests (t-test) were employed for pairwise or multiple comparisons of continuous variables. Spearman's correlation analysis was performed on the basis of the relationship between quantitative data. Additionally, simple linear regression analysis was performed to assess the relationship between ECG parameters and COHb levels. Because our study was planned as a retrospective study, power analysis was not performed because all data that met the inclusion criteria were included. A p value <0.05 was considered statistically significant. All data were entered into an Excel database (Microsoft Office 2010, Redmond, WA, USA), and statistical analysis was conducted using SPSS (IBM SPSS Statistics Version 22, SPSS Inc., Chicago, IL).

Results

Of the 102 patients initially included in the study, 28 who smoked, two who were pregnant, and four whose data were not clearly accessible were excluded from the study. Ultimately, a total of 68 patients were included in the study. The patients' mean age was 37.9 ± 13.71 years. They comprised 38.2% males and 61.8%. While 94.1% of the cases were caused by radiators, water heaters, combi boilers, solid fuel stoves such as wood and coal, and natural gas stoves, 5.9% occurred as a result of fire and exposure to exhaust gas. Fourteen patients (20.5%) had a history of chronic disease (1 coronary artery disease, 1 chronic COPD, 1 heart failure, 7 diabetes mellitus, 1 previous ischemic cerebrovascular disease history, and 3 a history of hypertension).

When the CO level was divided into two groups of very low and low, the very low level was proportionally higher in non-heater-related CO exposures concerning the source of poisoning, but it was statistically insignificant at p=0.06. When the patient groups with low and very low CO levels and the two groups with and without a history of chronic disease were separated, no significant difference was found between the groups (p=0.134).

The mean ECG PR distance was 210.59 ± 8.44 milliseconds, with a mean QRS distance of 84.97 ± 1.39 milliseconds, and a mean rate of 81.60 ± 8.50 beats per minute.

In 47 patients, the PR distance on ECG was longer than the normal range (120-200 ms). Sinus tachycardia >100 beats per minute was present in three of these patients. Notably, the QRS distance of all patients was within the normal range (<100 ms).

With regard to COHb levels of low-dose and very low-dose CO poisoning, ECG parameters (for PR interval, p=0.384; for QRS interval, p=0.342), blood parameters of troponin (p=0.338), lactate (p=0.676), pH (p=0.166), WBC (p=0.474), and neutrophil (p=0.341), no statistical difference was found, whereas a significant difference was revealed in terms of heart rate (p=0.001) between the groups (Table 1). There was a strong positive correlation between blood COHb level and heart rate (p=0.001, r=-0.823**). Regression analysis was performed between ECG heart rate and COHb level, and the linear regression equation was found to be y=2.38x+58.32 (r^2=0.68) (Figure 1). The mean level of lactate, troponin I, WBC, and neutrophils were 2.1 ± 1.5 (0-2 mmol/L), 10.9 ± 8.7 (2-14 ng/L), 9.9 ± 3.3 (4-10x100^3/uL), and 7.0 ± 3.0 (1.7-7.2 x100^3/uL), respectively (Table 2).

In the ROC analysis, The ECG parameters associated with CO poisoning are presented in Table 3 and Figure 2. Among these parameters, the power of heart rate to distinguish low- and very-low-dose CO poisoning at the optimum threshold level (79 beats/min) with a sensitivity of 0.97 and a specificity of 0.857 was stronger than the other two parameters [area under curve: 0.974, 95% confidence interval: (0.943-1.000), p<0.001].

Discussion

CO affects almost all organs and tissues, such as the brain, heart, kidneys, skeletal muscle, and peripheral nerves. Symptoms vary depending on whether the poisoning is acute or chronic and the CO concentration to which the poisoner is exposed (6,8). Regarding the etiology of CO poisoning, water heaters, combi boilers, solid fuel stoves such as catalytic and wood-coal-burning stoves, and natural gas stoves are the most common examples of these systems (9,10). This study is consistent with the literature, and cold seasons and water heater-related poisoning were present in the etiologies of most of our patients.

The main complications of CO poisoning are hypotension, angina, myocardial infarction, atherosclerosis, arrhythmias (sinus tachycardia, ventricular tachycardia and fibrillation, atrial flutter and fibrillation), and electrocardiographic changes (a decrease in the R wave size, ST elevation, T wave inversion, and heart blocks) (11).

Table 1. Comparison of ECG and blood parameters of patients with low- and very low-dose CO poisoning

	COHb 5-10%		COHb 10-15%		
	n	**mean ± SD**	**n**	**mean ± SD**	**p value**
PR interval (ms)	35	209.7 ± 8.2	33	211.5 ± 8.7	0.384
QRS interval (ms)	35	83.8 ± 1.4	33	85.2 ± 1.5	0.342
Heart rate (bpm)	35	75.4 ± 4	33	88.2 ± 6.9	0.001
Lactate	35	2.03 ± 1.21	33	2.19 ± 1.62	0.676
pH	35	7.41 ± 0.04	33	7.39 ± 0.05	0.166
Troponin I	35	8.04 ± 7.12	33	13.29 ± 9.74	0.338
White blood cell	35	9.55 ± 3.46	33	10.15 ± 3.16	0.474
Neutrophil	35	6.64 ± 2.51	33	7.37 ± 3.44	0.341

t-test, p<0.05, ECG: Electrocardiogram, CO: Carbon monoxide, COHb: Carboxyhemoglobin, pH: potential of hydrogen, SD: Standard deviation

A clinical study showed that all patients presenting to the hospital with moderate or severe CO poisoning should routinely undergo serial evaluation of ECG and cardiac markers, and those with positive signs of myocardial cytonecrosis or pre-existing ischemic heart disease should also undergo echocardiography (12).

In a study by Gandini et al. (13), transient myocardium and mitral valve function disorders were reported in a 12-year-old child who presented with an asymptomatic clinical picture and did not have a high COHb level.

In a study, it was indicated that cardiac performance was decreased and cardiac ischemia was increased in patients with underlying coronary artery disease and low-level CO poisoning (14). Another study reported that the angina threshold decreased in patients with coronary artery disease with low-level CO poisoning (6). In another study, it was stated that PR and QRS intervals on ECG were longer than normal in all patients with CO poisoning. Ischemia is believed to be the cause of this prolongation. Cell death, intracellular mitochondrial damage, and free radical formation as a result of CO poisoning is a known pathway of damage. This study argued that cellular damage secondary to hypoxia and free radical formation causes PR prolongation (15,16).

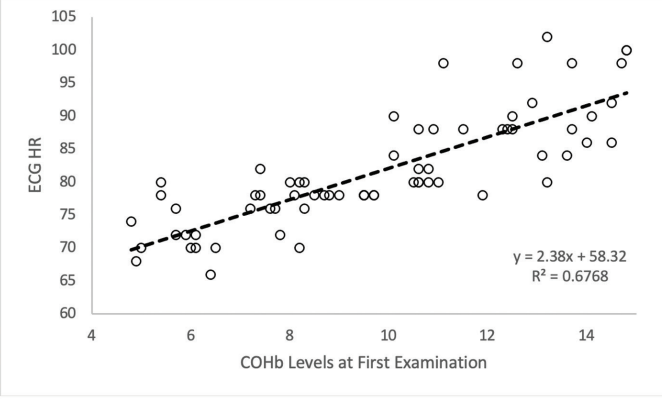

Figure 1. Regression analysis was performed between ECG heart rate and carboxyhemoglobin

ECG: Electrocardiogram, COHb: Carboxyhemoglobin

Table 2. The initial heart rate and blood parameters of patients at ED admission

n=68		Mean	SD ±
1	Heart rate	81.6	8.5
2	Lactate	2.1	1.5
3	Troponin I	10.9	8.7
4	White blood cell	9.9	3.3
5	Neutrophil	7.0	3.0
6	Carbon monoxide	9.8	2.9

ED: Emergency department, SD: Standard deviation

This study found that in low-dose asymptomatic CO poisoning, as the COHb level increased, the heart rate increased, and there was a very strong positive correlation, but no significant difference was determined in the PR and QRS intervals on ECG. The PR and QRS intervals on ECG differed at low and very low COHb levels in the ROC analysis. We believe that clinicians ignore and neglect this increase because it is not noticeable for patients in the clinic and because this increase on ECG is within the normal reference range in low-dose CO poisoning, but low doses of CO cause cardiac muscle cell damage due to CO affinity and tissue hypoxia, even in asymptomatic cases. Hence, we believe that studies with larger patient groups will contribute significantly to the literature on heart rate and ECG changes. It is known that cardiac scintigraphy is the preferred method for evaluating cardiac damage in patients after acute CO intoxication (17). We propose that cardiac scintigraphy can be used to diagnose cardiac damage caused by low-dose CO poisoning.

Eichhorn et al. (18) found a relationship between CO poisoning and troponin I value and revealed that there might be a correlation between the severity of CO poisoning and myocardial damage. Another study reported that troponin I was effective in demonstrating cardiac damage in symptomatic patients with CO poisoning admission (19). A study by Ilano and Raffin (6) reported that the angina threshold decreased in patients with coronary artery disease who experienced low-level CO poisoning.

When CO is at toxic levels, thrombosis is increased. Increasing the expression of inducible nitric oxide (NO) synthase, it increases

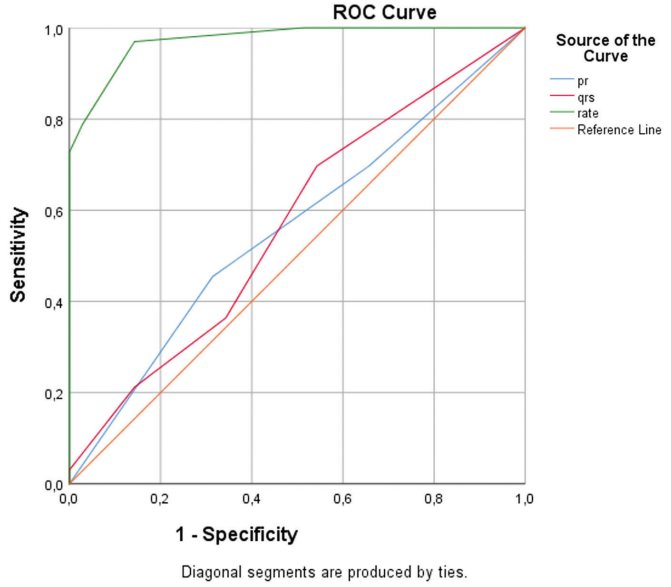

Figure 2. ROC curve analysis. The data show that heart rate has a higher power to discriminate low and very low COHB levels than PR distance and QRS interval

ROC: Receiver operating characteristic, COHb: Carboxyhemoglobin

Table 3. Comparison of the ability of ECG parameters to predict low- or very-low-dose COHb levels

Factor	AUC	CI 95% Lower-upper	Sensitivity	Spesificity	Youden index	Cut-off
Heart rate (beats/min)	0.974	0.943-1.000	0.970	0.857	0.827	79.00
PR interval (ms)	0.560	0.422-0.697	0.555	0.686	0.240	215.00
QRS interval (ms)	0.569	0.432-0.707	0.697	0.457	0.154	84.50

AUC: Area under curve, CI: Confidence interval, ECG: Electrocardiogram, COHb: Carboxyhemoglobin

NO-related myocardial damage that occurs during ischemia-reperfusion (20).

In the present study, we found that cardiac troponin I values did not statistically significantly differ in very low and low-dose CO poisoning and were within the normal reference range, but troponin I values were different between low- and very low-dose CO poisoning, although they were insignificant. However, hs-troponin has a higher affinity for detecting cardiac damage than normal troponins (21). Therefore, we conclude that hs-troponin examination will be more sensitive in detecting cardiac damage, even in asymptomatic low-dose CO poisoning cases. Approximately 10-15% of CO is extravascular and bound to molecules such as myoglobin, cytochromes, and NADPH reductase, leading to impairment of oxidative phosphorylation at the mitochondrial level.

CO causes anaerobic glycolysis and lactate production by causing tissue hypoxia. Moreover, CO has systemic effects that may lead to lactate production, including seizures, hyperventilation, and cardiac dysfunction (22,23). We found that lactate levels and pH were within the normal reference range because hyperventilation and serious cardiac damage did not occur because our study model included low-dose CO poisoning. Although these values differed between low-dose and very low-dose CO poisoning, no statistically significant difference was observed.

CO has a toxic effect on hypoxia and inflammation. Additionally, CO exposure causes inflammation in many ways other than hypoxia. Inflammation caused by oxidative factors and cytokines is a response to damaging stimuli. Different parameters indicate inflammation. Circulating white blood cells and neutrophils increase in response to inflammation. Troponin levels increase during cardiac injury, whereas lactate increases secondary to anaerobic glycolysis in tissues and increases secondary to inflammation (5,24). Although there was no statistical difference between the mean lactate, troponin, WBC, and neutrophil levels in low- and very low-dose CO poisoning, these inflammatory biochemicals had higher values in low-dose CO poisoning. Therefore, we believe that as the COHb level increases, inflammatory markers, such as troponin, lactate, white blood cells, and neutrophils, increase in a correlated manner, and many mechanisms, such as inflammation, glycolysis, and cardiac damage, are effective. We propose that histopathological studies be conducted to reveal the cellular damage caused by these changes in biomarkers detected in low-dose poisoning cases.

Study Limitations

This study has some significant limitations. This was a retrospective study. Thus, other factors influencing heart rates and clinic changes over time are missing. More extensive and long-term prospective cohort studies are needed to confirm the causal link between heart rate and COHb levels. Furthermore, the study's single-center design may restrict the generalizability of the results. The necessity of conducting studies with larger patient groups arises because of the retrospective nature of our study and the limited number of cases.

Conclusion

In conclusion, it should be kept in mind that patients may sometimes present with low COHb levels in the clinic. If patients have available ECGs, they should definitely be compared with their previous ECGs, and blood parameters, especially lactate, troponin, WBC, and neutrophil levels, should be evaluated. It should not be forgotten that tissue and organ damage can occur with low-dose poisoning. Early diagnosis and treatment are important for preventing tissue and organ damage.

Ethics

Ethics Committee Approval: The study was initiated with the approval of the Niğde Ömer Halisdemir University Non-Invasive Clinical Research Ethics Committee (decision number: 2023/56, date: 24.08.2023).

Informed Consent: This retrospective study.

Authorship Contributions

Surgical and Medical Practices: T.D., Concept: T.D., Design: T.D., A.V., Data Collection or Processing: T.D., A.V., Analysis or Interpretation: T.D., A.V., Literature Search: T.D., A.V., Writing: T.D., A.V.

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