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Macro-CK in carbon monoxide poisoning: A guide for in-hospital mortality?

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Abstract

Carbon monoxide (CO) poisoning is common in developing countries and can be mortal. CO poisoning can present with various signs and symptoms. In addition, it has been observed that some people have increased cardiovascular diseases and are associated with high mortality. In this study, the usability of Macro creatine-kinase (Macro-CK) for in-hospital mortality detection in CO poisoning was investigated. This study is a retrospective and single-center study. Data of patients diagnosed with CO poisoning were accessed from the hospital automation system. Macro-CK was accepted for patients with CK-MB higher than total CK. The patients were divided into two groups according to the Macro-CK determination. Macro-CK detected patients were arranged as group-1, and the others as group-2. In-hospital mortality rates were determined in the groups and compared between groups and analyzed. 1100 patients were eligible for the study. Of these patients, Macro-CK was detected in 33 patients (0.03%). The mean age of the patients was 37.6 ± 16.9 and 43.2% were male. In-hospital mortality was 20 (60.6%) in group 1, and 50 (4.7%) in group 2 and was statistically significant ($p<0.001$). As a result of the regression analysis, it was determined that Macro-CK was statistically significant with in-hospital mortality ($p=0.001$). This result shows us that as the Macro-CK increases, the mortality also increases. Our study is the first study in the literature investigating the relationship between Macro-CK and mortality in CO poisoning. It is a study in which Macro-CK is determined as an independent predictor of in-hospital mortality.

Keywords: Poisoning, cardiotoxic, mortality, creatine kinase, toxicity

Introduction

Carbon monoxide (CO) is an odorless, tasteless and colorless gas that emerges from incomplete combustion of fossil fuels and is the most common cause of death due to poisoning in the world [1, 2]. Inhaled CO combines with hemoglobin and myoglobin in 85% and 15%, retrospectively, and its ability to bind to hemoglobin is approximately 220 times higher than oxygen [3]. Due to the binding of CO to the heme protein in hemoglobin, carboxyhemoglobin (COHb) is formed, causing the oxyhemoglobin dissociation curve to shift to the left, reducing the oxygen carrying capacity to tissues [4]. As a result, various symptoms and signs occur in the patients. CO poisinoning, which first presents with nonspecific signs and symptoms such as weakness, fatigue, headache, dizziness, nausea, vomiting, and when the COHb level reaches 20-30%, severe intoxication signs and symptoms such as syncope, seizure, arrhythmias, respiratory failure and coma can be seen [5-7].

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CO gas is cardiotoxic. CO binds to myoglobin, causing electrical, functional and morphological changes in the heart, and by binding to hemoglobin, it causes myocardial damage by creating hypoxia [3, 8]. This myocardial damage has been shown to occur when the COHb level is between 37-53% [8]. Also, a wide range of arrhythmias such as sinus tachycardia, atrial flutter and fibrillation, blocks, ventricular premature beats, ventricular tachycardia and fibrillation can be observed [9]. Depending on the degree of coronary hypoperfusion, creatine kinase (CK), creatine kinase isoenzyme (CK-MB) and troponin levels may increase [3, 10, 11]. In some patients, CK-MB may increase more than total CK. In this case, we can talk about the existence of the Macro-CK. Macro-CK can occur due to malignancies, liver diseases and during the process with immunoglobulins [12]. In some studies, it has been emphasized that Macro-CK increases in cardiovascular diseases and is associated with high mortality [11-14].

According to our literature search, there are no studies investigating the relationship between Macro-CK and mortality in CO poisoning. With this study, we aimed to determine the increase in Macro-CK in CO poisoning and to investigate its relationship with in-hospital mortality.

Materials and Methods

Study Design and Patients Selections

A retrospectively cross-sectional study was conducted in a third level university hospital. An ethical approval was obtained from the local ethics committee for the study (data: 27.12.2018; no: 08/44). The data of the patients were accessed and searched from hospital automation system. The inclusion criteria for the study were those who were diagnosed with CO poisoning between 2012 and 2018 and were 18 years of age or older.

The exclusion criteria of the study were patients whose file records could not be reached, those under 18 years of age, patients with autoimmune disease, malignancy, and liver disease.

During the time the study was planned, 1562 patients diagnosed with CO poisoning were retrospectively identified. After applying the inclusion and exclusion criteria of the study, 1100 patients were included the study. While determining the study groups, patients were divided into two groups according to the Macro-CK determination. Group 1 consists of patients whose presence of Macro-CK could not be detected, while group 2 consists of patients with the presence of Macro-CK.

Data collection and measurement

The age, gender, number of days of hospitalization, in-hospital mortality, COHb level, blood gas parameters, liver and kidney function tests, CK, CK-MB, Macro-CK and troponin values of the patients included in the study, were recorded and analyzed.

Macro-CK

Since Macro-CK has a high molecular mass, it cannot be measured by quantitative methods and cannot be distinguished from total CK. The Macro-CK level can be measured by electrophoretic, chromatographic or immuno-inhibition methods [13]. If the CK-MB isoenzyme constitutes more than 50% of the total CK, Macro-CK elevation can be mentioned [13].

Our study, on the other hand, is a retrospective study and Macro-CK level could not be measured by other methods. If CK-MB is higher than total CK, it is accepted as Macro CK.

COHb measurement

For the measurement of COHb, venous blood samples taken from patients with the heparin injectors were studied with Radiometer ABL800 FLEX blood gas analyzer in the biochemistry unit.

Outcomes of the study

The primary outcome of this study is to investigate the relationship between Macro-CK and mortality in CO poisoning. The secondary outcome is to determine the Macro-CK increase in CO poisoning.

Statistical Analysis

All statistical studies were carried out with the SPSS program (version 20.0, SPSS, Chicago, Illinois, USA). Categorical data was presented as counts and proportions. We described continuous data as mean values and standard deviation (SD) or median values and interquartile range (IQR), based on distribution of data. Categorical variables were compared using Chi-squared or Fisher exact tests, as appropriate. The Student t-test was used if the groups compared were two groups and the normally distributed, and the Mann Whitney U test if it was not normally distributed. Logistic regression analysis was used to identify the independent predictors of in-hospital mortality. Two-tailed p values <0.05 were considered as statistically significant.

Results

Participants

A total of 1562 patients with CO poisoning were included in the study. According to the inclusion and exclusion criteria of the study, 1100 patients were eligible for the study. Macro-CK was detected in 33 patients (0.03%) of these participants and was determined as group 2. There were 1067 patients in group 1 (Figure 1).

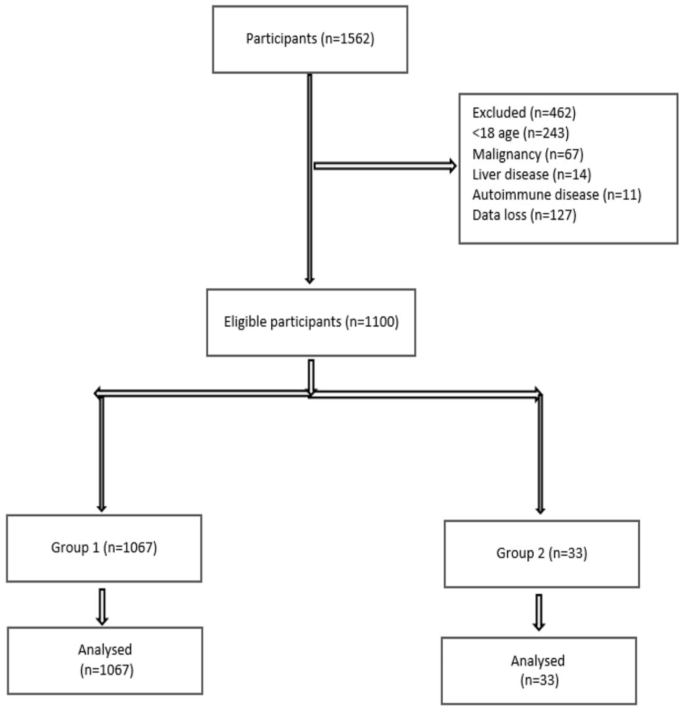

Figure 1. Flow chart of the study

General Features of the Patients

The mean age of the patients was 37.6 ± 16.9 years and 43.2% were male. Average hospitalization duration was 5.3 days. The patients most frequently applied to the hospital with the complaint of headache (34.3%). The patients' admission COHb value was 9.4% (2.7-19). The socio-demographic and laboratory characteristics of the patients are shown in Table-1.

Comparison of the groups

The average age of the groups were 37.8±17; 32.1±13.4 years, respectively; and was not statistically significant (p> 0.05). The hospitalization duration of the patients in group 2 was longer and was also statistically significant (p = 0.030). In-hospital mortality rates were 4.7% (n=50), and 60.6% (n=20), respectively, and was

statistically significant (p <0.001). In blood gas analysis, pH level was lower and COHb level was higher in group 2 than the group 1, and it was statistically significant (p< 0.05). The demographic and clinical comparative analysis of both groups are given in Table-2.

Table 1. Socio-demographic characteristics and laboratory parameters of patients

Variables	Mean ± SD, n (%)
Age, (years), mean ± SD	37.6±16.9
Sex, male, n (%)	475 (43.2)
Chronic diseases, n (%)	139 (12.6)
Hypertension	56 (5.1)
Heart Diseases	35 (3.2)
Diabetes mellitus	24 (2.2)
Pulmonary Diseases	17 (1.5)
Chronic renal failure	7 (0.6)
Symptoms/signs, n (%)	
Headache	378 (34.3)
Nausea	233 (21.2)
Vomiting	147 (13.4)
Vertigo	101 (9.2)
Dyspnea	47 (4.3)
Confusion	28 (2.5)
Seizures	19 (1.7)
Syncope	18 (1.6)
Other	129 (13.4)
Hospital stay (day), median (IQR)	3.6 (1.1-2.4)
Mortality, n (%)	70 (6.4)
pH, mean ± SD	7.38 ± 0.3
PCO2 (mmHg), mean ± SD	39.8 ± 6.8
COHb (%), median (IQR)	7.1 (3.4-20)
Lactat (mmol/L), median (IQR)	1.8 (0.4-2.5)
Creatinine (mg/dL), median (IQR)	0.89 (0.6-1.4)
Glucose (mg/dL), median (IQR)	111.9 (88.9-150.5)
Na (mmol/L), median (IQR)	138.9 (134.9-142.9)
K (mmol/L), median (IQR)	4.8 (4.3-5.1)
Ca (mmol/L), median (IQR)	10.2 (8.6-11.2)
P (mmol/L), median (IQR)	3.4 (2.9-4.5)
WBC (10^3 /µL), median (IQR)	9.5 (7.4-14)
HG (g/dL), mean ± SD	14.1 ± 2.1
PLT (10^3 /µL), median (IQR)	247.8 (189.4-292.3)
Albumin (mg/dl), mean ± SD	4 ± 0.5
AST (UI/L), median (IQR)	26.1 (16.9-39.2)
ALT (UI/L), median (IQR)	22.3 (13-33.5)
LDH (ng/mL), median (IQR)	239.9 (184.3-403.5)
Troponin I (ng/mL), median (IQR)	0,24 (0.01-1.2)
CK (ng/mL), median (IQR)	220 (58.2-478.5)
CK-MB (ng/mL), median (IQR)	33 (13.1-90.2)

Note: COHb: carboxyhemoglobin; Na: sodium; K: potassium; Ca: calcium; P: phosphorus; WBC: white blood cell; HG: hemoglobin; PLT: platelets; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; CK: creatine kinase; CK-MB: creatine kinase-MB

Table 2. Comparisons of the groups

Variables	Group-1 (n=1067)	Group-2 (n=33)	P value
Age, (years), mean ± SD	37.8±17	32.1±13.4	0.173
Sex, male, n (%)	454 (42.6)	21 (63.2)	0.073
pH, mean ± SD	7.38±0.02	7.33±0.21	0.036
PCO2 (mmHg), mean ± SD	39.8±6.8	40.7±6.5	0.427
COHb (%), median (IQR)	7 (3.4-20)	9.5 (2.7-19)	0.006
Lactate (mmol/L), median (IQR)	1.8 (0.4-2.5)	2 (1.3-2.4)	0.836
Hospital stay (day), median (IQR)	3.5 (1.1-2.4)	5.4 (1.1-3.7)	0.030
Mortality, n (%)	50 (4.7)	20 (60.6)	<0.001
Creatinine (mg/dL), median (IQR)	0.9 (0.6-1.4)	0.7 (0.5-1.1)	0.346
Glucose (mg/dL), median (IQR)	112 (89-151)	109 (87-134)	0.703
Na (mmol/L), median (IQR)	139 (135-143)	136 (132-138)	0.601
K (mmol/L), median (IQR)	4.8 (4.3-5.1)	4.3 (3.4-4.8)	0.275
Ca (mmol/L), median (IQR)	10.2 (8.6-11.2)	9 (7.5-9.9)	0.482
P (mmol/L), median (IQR)	3.4 (2.9-4.5)	3.2 (2.9-3.8)	0.323
WBC (10^3 /µL), median (IQR)	9.5 (7.4-14)	10.7 (8.2-13)	0.190
HG (g/dl), mean ± SD	14.08±2.1	14.8±1.3	0.087
PLT (10^3 /µL), median (IQR)	248 (190-292)	241 (170-302)	0.691
Albumin (mg/dL), mean ± SD	4±0.5	4.3±1.4	0.078
AST (UI/L), median (IQR)	26 (17-39)	30 (15-47)	0.072
ALT (UI/L), median (IQR)	22 (13-33)	33 (14-49)	0.154
LDH (ng/mL), median (IQR)	237 (182-403)	335 (259-421)	0.035
Troponin I (ng/mL), median (IQR)	0.23 (0.01-1.2)	0. 50 (0.1-1.1)	0.094
CK (ng/mL), median (IQR)	225 (59-490)	61 (34-108)	<0.001
CK-MB (ng/mL), median (IQR)	25 (12-75)	290 (48-580)	<0.001

Note: COHb: carboxyhemoglobin; Na: sodium; K: potassium; Ca: calcium; P: phosphorus; WBC: white blood cell; HG: hemoglobin; PLT: platelets; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; CK: creatine kinase; CK-MB: creatine kinase-MB

Mortality and Macro-CK

The Macro-CK values of the deceased were higher as given in Figure 2. This result shows that as the Macro-CK increases, the mortality also increases. This situation was also found to be statistically significant (p = 0.001).

A model was created between age, pH, Macro CK, COHb and LDH variables and mortality by logistic regression. Logistic regression was performed using the Enter model. As a result of the regression analysis, it was determined that Macro-CK was statistically significant with in-hospital mortality (p = 0.001) (Table 3).

Table 3. In-hospital mortality and logistic regression analysis results

Variables	OR, 95%CI	P value
Age (years)	1.02 (0.95-1.2)	0.932
pH	0.89 (0.78-1.05)	0.079
Macro-CK	2.3 (1.5-3.4)	0.001
COHb	1.2 (1.01-1.6)	0.050
LDH	1.19 (0.97-1.5)	0.311

Note: COHb: carboxyhemoglobin; LDH: lactate dehydrogenase

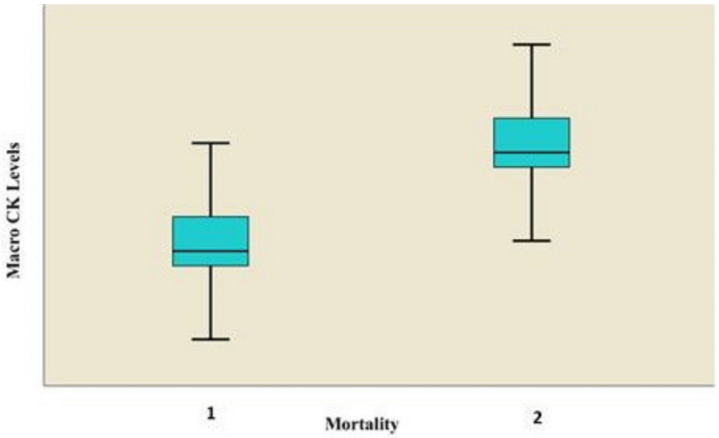

Figure 2. Macro-CK and mortality boxplot figure

Discussion

In this study, the presence of Macro-CK in patients with CO poisoning and its relationship with in-hospital mortality was investigated. Macro-CK was detected in 33 of the patients included in the study. COHb level was higher in Macro-CK group and it was statistically significant (p<0.05).

In-hospital mortality rate was higher in the patient group with Macro-CK and was statistically significant ($p < 0.001$). As a result of the logistic regression analysis, it was confirmed that Macro-CK presence was statistically related with in-hospital mortality ($p = 0.001$).

In CO poisoning, CO gas binds to hemoglobin with 200-250 times more affinity than oxygen, shifting the oxyhemoglobin dissociation curve to the left, reducing oxygen delivery to tissues and causing deep hypoxia [15]. It also binds to myoglobin in heart and muscle tissue and other proteins containing heme, including cytochrome c oxidase, causing toxicity by affecting cellular respiration [16, 17]. As a result of this toxicity, the brain and heart with the highest sensitivity to hypoxia can be severely affected and cardiac biomarkers may increase according to the degree of toxicity [4, 15].

CK is an enzyme that is a member of the kinase family, which is detected in low levels in plasma, but also in other tissues such as kidney, brain and intestine. Three isoforms are defined. The CK-MB form is specific to the heart and increases rapidly during acute myocardial infarction and reaches a highly detectable level in plasma. While the plasma CK-MB level constitutes 5% of the CK level in normally, this rate changes in myocardial infarction [18].

In cases where plasma CK-MB level is measured above total CK, Macro-CK status is mentioned. Macro-CK is a macro protein complex that cannot be detected by standard measurement methods but, can be easily detected by immunoinhibition or electrophoresis methods [12, 19]. Two types of Macro-CK have been identified [13, 19], type 1 is associated with immunoglobulins, type 2 is associated with malignancy and liver diseases [12]. Therefore, in our study, in order to detect the relationship between Macro-CK and the CO poisoning, we were excluded the patients with malignancies and liver diseases.

Studies in the literature have found that mortality increases significantly in patients with myocardial damage in CO poisoning [11, 20]. In a study investigating the relationship between myocardial injury and long-term mortality in patients with moderate and severe CO poisoning, it was found that 37% of the patients had myocardial injury and 38% of them died in an average of 7.6 years [11]. In that study, it was stated that high troponin value predicts long-term mortality in CO poisoning. In another study conducted by Satran D et al., it was emphasized that CK-MB or troponin I biomarkers increased in 35% of the patients and the in-hospital mortality rate was 5% [20]. However, there are no studies in the literature investigating Macro-CK in patients with CO poisoning.

In our study, Macro-CK was investigated for the first time in the literature. Although long-term mortality was not considered, it was determined that Macro-CK was predictive in in-hospital mortality, while high troponin value was not predictive. Therefore, it was revealed that the presence of Macro-CK in patients with CO poisoning is a poor prognostic indicator. This situation may have been caused by the increased level of macro proteins and the decrease in the oxygen level delivered to the tissues due to hyperviscosity. In patients with poor tissue oxygenation due to CO poisoning, and an additional burden of hyperviscosity may increase tissue hypoxia and increase mortality. It is seen as a result of our study that patients with Macro-CK need more aggressive treatment.

Limitations

Our study has some limitations. Since it is a retrospective study, Macro-CK could not be measured by electrophoretic, chromatographic or immuno-inhibition methods. In addition, Macro-CK subtypes could not identified in patients with Macro-CK. In our study, only in-hospital mortality was examined, but long-term mortality was not investigated.

Conclusion

Our study is the first study in the literature investigating the relationship of Macro-CK with mortality in CO poisoning. Macro-CK was found to be as an independent predictor of in-hospital mortality. In the further studies, prospective investigation of Macro-CK levels and subtypes should be measured by electrophoretic, chromatographic or immuno-inhibition methods.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
Atatürk University Faculty of Medicine Clinical Research Ethics Committee-data:27.12.2018; number:08/44.

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