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Copeptin levels in carbon monoxide poisoning

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Background/aim: The aim of this study is to identify the copeptin levels in patients presenting with carbon monoxide (CO) poisoning to the emergency department and to investigate its correlation with the neurological effects.

Materials and methods: The study group consisted of patients presenting with CO poisoning and carboxyhemoglobin levels >10%. Blood samples for copeptin levels were obtained twice, first at presentation then at the fourth hour of observation. The data were analyzed using SPSS 16 for Windows.

Results: The median copeptin levels of the patient group were identified as 0.63 (0.39–1.06) ng/mL at hour 0 and 0.41 (0.31–0.49) at hour 4. The copeptin levels of the control group were 0.34 (0.25–0.42) ng/mL and were significantly lower than those of the patient group ($P < 0.000$). According to our results, 0.345 ng/mL for plasma copeptin level as the best cut-off level may be used with sensitivity of 94.0% and specificity of 60%. The copeptin levels at hour 0 were statistically significantly higher in the neurologically affected patients than those not affected ($P < 0.001$).

Conclusion: In this study it was shown that blood copeptin levels increase in patients presenting to the emergency department with CO poisoning.

Key words: Carbon monoxide poisoning, copeptin, neuromarker

1. Introduction

Carbon monoxide (CO) poisoning is a health problem that frequently occurs in Turkey and worldwide. In Turkey, it accounts for 30% of the poisoning cases that end with death (1).

This colorless, odorless, tasteless, and nonirritating gas is produced as a result of the incomplete burning of organic matter that can easily be absorbed by the lungs. CO poisoning can cause cerebral, cardiac, and general ischemia. The poisoning can be diagnosed according to the blood carboxyhemoglobin (COHb) levels. There is a weak correlation between blood COHb levels and organ damage. Poisonings higher than 60% end with death and at lower levels clinical findings range from mild to severe. It is not always possible to identify this using the COHb level (2). Biochemical markers other than COHb are being studied to identify the clinical outcomes of this poisoning with neurotoxic and cardiotoxic effects in particular (3).

Copeptin is excreted from the posterior hypophysis simultaneously with vasopressin and reflects the amount of vasopressin in circulation. Copeptin is more stable than vasopressin in plasma and serum. Studies conducted have reported that copeptin and vasopressin levels float parallel to each other both in healthy individuals and in the critically ill patient population. Recently copeptin has been investigated as a diagnostic and prognostic factor in many diseases like pneumonia, heart failure, and hemorrhagic and septic shock and it has been identified that its levels rise in correlation with the severity of the disease (4–7).

The aim of this study is to identify the copeptin levels in patients presenting to the emergency department with CO poisoning and to investigate its correlation with neurological damage.

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2. Materials and methods

This study is a prospective controlled study conducted in the emergency department of the Ankara Keçiören Training and Research Hospital after obtaining permission from the local ethics board. Patients presenting to the emergency department with a clinical picture of CO poisoning between November 2012 and April 2013 with COHb levels higher than 10% that agreed to participate in the study were included in the study. The control group was selected from healthy volunteers of the same age group consistent with the study population. Patients under 18 years of age, kidney failure cases, patients using corticosteroids, and pregnant patients were excluded from the study. The demographic characteristics, CO source, time to arrival to the emergency department, presentation complaints, and systemic and neurological findings were recorded on the form prepared. The patients with a history of syncope, convulsion, Glasgow coma score (GCS) of <15 at presentation, and neurological deficits were regarded as neurologically affected. Patients were treated with normobaric (NBOT) or hyperbaric (HBOT) oxygen therapy accordingly. The HBOT indications were syncope, loss of consciousness, seizures, coma, blood COHb levels >25%, focal neurological deficits, and findings of acute myocardial ischemia. The other patients were administered 100% NBOT with a reservoir mask in the emergency department. Blood samples were taken twice, at presentation and the fourth hour of observation.

2.1. Blood specimen measurement

The blood samples for copeptin levels were taken at the time when patients were first admitted to the emergency department and 4 h after the patient's initial admission. The blood samples for copeptin levels were taken into tubes used for biochemistry samples and were centrifuged. Centrifuged blood samples were kept at –80 °C until all blood samples were obtained. The blood samples were analyzed using the manual ELISA immunoassay method with copeptin kits.

2.2. Statistical methods

The analysis of the data was done using SPSS 16 for Windows. The consistency of truncated and continuous variables with normal distribution was investigated using the Kolmogorov–Smirnov test. Descriptive statistics were expressed as mean ± standard deviation or median (minimum–maximum) for truncated and continuous variables and as the number of cases and (%) for categorical variables.

The presence of statistically significant changes in the mean values of the patient and control groups was evaluated using the independent double sample t-test and median values of data not consistent with normal distribution were evaluated using the Mann–Whitney U test. $P < 0.05$ was set for statistically significant results. Receiver operating characteristic (ROC) curves were configured to establish the cut-off point of the plasma copeptin level with the calculated area under the curve (AUC) and 95% confidence interval. $P < 0.05$ was considered significant.

3. Results

The study was conducted with 51 patients exposed to CO who met the inclusion criteria and 48 healthy volunteers with a similar age and sex distribution. Most of the presentations occurred between 0000 and 0400 hours at a rate of 27.5% and most of the poisonings were caused by gas (39.2%). The mean COHb levels were 30.11 ± 6.71% at presentation and 7.46 ± 3.22% at hour 4. Eight patients received HBOT and 43 received NBOT (Table 1).

The mean copeptin levels of the patient and control groups are shown in Table 2. The drop in the copeptin levels that occurred at hour 4 after observation and treatment was statistically significant when compared to the baseline levels (hour 0) ($P < 0.000$) (Table 2).

The validity of the tests was evaluated by an analysis of ROC curves. The ROC curve identified that a plasma copeptin level of >0.345 ng/mL predicted patients with 94% sensitivity and 60% specificity, while the positive predictive value was 70% and the negative predictive value was 90% (AUC: 0.856; 95% confidence interval: 0.785–0.927) (Figure).

While the copeptin levels at hour 0 of patients neurologically affected after carbon monoxide poisoning (syncope, convulsions, etc.) were significantly higher than those of patients not neurologically affected, there was no statistically significant difference in the levels of copeptin at hour 4 between the groups (respectively $P <0.000$ and $P = 0.057$) (Table 3).

4. Discussion

The toxicity caused by CO inhalation is a condition that might cause permanent damage to tissues with high oxygen consumption like the brain or heart and may be fatal as it causes generalized and cerebral hypoxia. Many acute or late neurological/psychiatric disorders can develop after CO poisoning. In the acute period, early symptoms like headaches, nausea, and loss of concentration may develop. As the duration of exposure increases syncope, confusion, epileptic seizures, and coma may occur. Patients may also present with symptoms of acute stroke (8). In the late period of CO poisoning 'delayed neuropsychiatric syndrome' may develop weeks after the findings of acute intoxication disappear. It is predicted that this syndrome develops in 10%–30% of patients (8). Many biomarkers have been investigated to predict the neurological damage occurring in the acute and late phases of CO poisoning. Yardan et al., who investigated serum S100B and neuron-specific enolase (NSE), reported that these markers were

Table 1. The demographic characteristics of the patients.

Age, years Mean ± SD (minimum–maximum)	 41.41 ± 17.69 (18–83)
Sex, n (%) Male Female	 23 (45.1%) 28 (54.9%)
CO source, % Gas Stove Gas water heater	 39.2% 33.3% 27.5%
Time to arrival to the emergency department, minutes Mean ± SD (minimum–maximum)	 23.14 ± 22.9 (10–120)
COHb level, % Median (minimum–maximum)	 29.8 (17.9–53.7)
Presentation symptoms, % Headache Nausea Dizziness Vomiting Syncope Confusion	 80.4% 62.7% 52.9% 27.5% 9.8% 5.9%
GCS score Mean ± SD (minimum–maximum)	 14.98 ± 0.14 (14–15)
HBOT, n (%) NBOT, n (%)	8 (15.7%) 43 (84.3%)

COHb: Carboxyhemoglobin, CO: carbon monoxide, GCS: Glasgow coma score, NBOT: normobaric oxygen therapy, HBOT: hyperbaric oxygen therapy.

Table 2. The copeptin levels of the patient and control groups at presentation (hour 0) and the copeptin levels of the patient group at hour 4.

	Carbon monoxide group	Control group	P
Hour 0 copeptin, ng/mL Median (IQR 25–75)	0.63 (0.39–1.06)	0.34 (0.25–0.42)	<0.001
Hour 4 copeptin, ng/mL Median (IQR 25–75)	0.41 (0.31–0.9)		
P	<0.001		

useful in evaluating the hypoxic brain damage in CO poisoning, especially in unconscious patients (9). Brvar et al. identified higher S100B levels in patients with GCS of ≤8 at presentation to the emergency department (10). Akdemir et al. identified higher S100B and NSE levels in all patients, conscious or unconscious, and higher glial fibrillary acidic protein (GFAP) levels only in unconscious patients in their study that evaluated S100B, NSE, and GFAP levels. The authors proposed that these three markers are useful in evaluating the severity of CO poisoning (11).

Copeptin is a stress hormone synthesized together with vasopressin and it is a new diagnostic biomarker for patients presenting with acute diseases (12). In this study it was found that the copeptin levels were significantly higher in CO-poisoned patients than the control group. In addition, the blood copeptin levels after treatment at hour 4 were significantly lower than the levels at presentation.

According to our results, 0.345 ng/mL for plasma copeptin level as the best cut-off level may be used with sensitivity of 94.0% and specificity of 60%. However, our

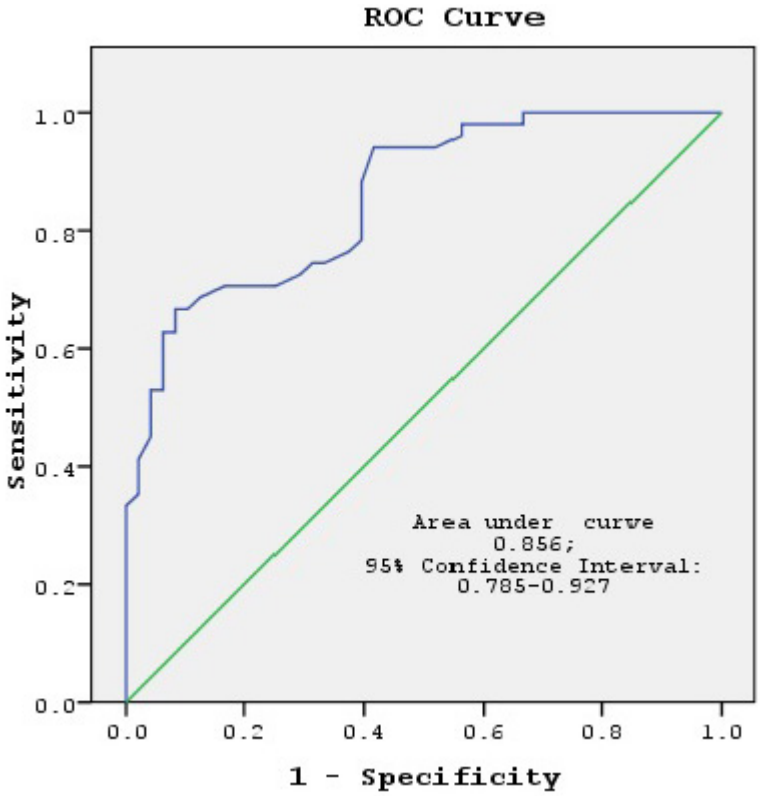

Figure. Graph showing the predictive significance of hour 0 plasma copeptin level for carbon monoxide (CO) poisoning. Receiver operating characteristic (ROC) curve was constructed based on the sensitivity and specificity of the plasma copeptin concentration for CO poisoning. The area under the curve was calculated based on the ROC curve and expressed as a 95% confidence interval. For the accuracy of the test, a value of 1.0 represents 100% sensitivity and specificity, and a value of 0.5 indicates no discriminatory power.

Table 3. The copeptin levels of patients with and without neurological findings.

	Patients with neurological findings Median (IQR 25–75)	Patients without neurological findings Median (IQR 25–75)	P
Hour 0 copeptin, ng/mL Median (IQR 25–75)	1.48 (1.32–4.66)	0.56 (0.37–0.81)	<0.001
Hour 4 copeptin, ng/mL Median (IQR 25–75)	0.49 (0.35–0.83)	0.41 (0.30–0.47)	0.057

cut-off level and control median values are very close; therefore, a higher level of copeptin may be considered in clinical practice.

Copeptin has been used as a diagnostic and prognostic neuromarker in many studies in the past years (13,14). It has been shown that copeptin is a reliable marker for predicting long-term outcomes, particularly in ischemic stroke. It has been shown that the prognostic value of copeptin in predicting the 1-year mortality and morbidity in stroke patients increases when the National Institutes of Health Stroke Scale is added. Although copeptin is not a specific marker, unlike other neuromarkers it directly bypasses the blood–brain barrier and is excreted into systemic circulation and thus it reflects the intracerebral condition better (14). A significant correlation has been shown between copeptin levels and prognosis and the GCS at presentation, not only in patients presenting with ischemic stroke but also for acute intracerebral hemorrhages (15).

Although the number of patients affected neurologically is low in the study that we are presenting, the copeptin levels of the neurologically affected patients at hour 0 were statistically significantly higher than those of patients not neurologically affected. However, we did not find a statistically significant difference in the level of copeptin at hour 4 between these groups. We think that this resulted from the significantly decreased copeptin levels in all patients after treatment. To our knowledge, there is only one related study on CO poisoning in the literature (16). In that study, conducted by Pang et al., the severity of the poisoning and the copeptin levels were evaluated in CO-poisoned patients. They identified higher copeptin levels in patients with lower GCS. In the same study, it was found that the copeptin levels were higher in patients that developed delayed neurological sequelae. As a result of that study, it was stated that copeptin can be used in CO poisoning, particularly in the diagnosis and observation of cerebral damage (16).

In the study that we conducted it was observed that the copeptin levels at hour 4 had significantly dropped in patients that had received O_2 therapy. Thus, we think that copeptin levels may also be used in evaluating the efficacy of oxygen therapy in patients presenting with CO poisoning.

The present study had several limitations. Our study is a single-center study and included a small number of cases. In addition, the study did not measure other plasma neuromarkers such as NSE levels, so it did not evaluate the relationship between those levels and copeptin levels in the patients with neurological findings in CO poisonings.

In conclusion, it was observed that blood copeptin levels rise in patients presenting to the emergency department with CO poisoning. We think that this stress hormone can be used as a diagnostic and monitoring tool in CO poisonings, particularly in detecting neurological damage. Our study was conducted with a small patient group and studies with larger patient groups are required.

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