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RESEARCH ARTICLE

Matrix Metalloproteinase-9, Neuron-specific Enolase, S100 B and Tau Protein Levels in the Patients with Carbon monoxide Poisoning

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Abstract:

Background:

S100B, NSE, MMP-9, and Tau protein levels increase in cases causing hypoxic cell damage. The diagnosis of the severity of carbon monoxide (CO) poisoning in the early period of these parameters was studied.

Material and Methods:

COHb level measurement was made using a signal capture CO-pulse oximeter (Masimo's SET Rainbow, Masimo's Co, USA) at the first admission of the patients. Then, COHb levels were confirmed by arterial blood gas(ABG) analysis. The patients were divided into two groups as mild and moderate-severe, according to their Glasgow coma scores (GCS) [Mild (14–15); Moderate (9–13) or Severe (3–8)]. The control group was composed of 16 healthy and non-smoking volunteers.

Results:

The serum S100B protein and MMP-9 values at 0 hr of admission in the hospital and 3hr of treatment were not significantly different in the patient group as compared to the control group. Tau protein levels were significantly higher in the patient group at 0 and 3 hours ($p > 0.05$) as compared to healthy person.

Conclusion:

There was no relationship between CO poisoning and MMP-9 and S100B protein levels. NSE and Tau protein were significantly higher in the patient group than the control group. Tau protein may be more useful marker as compared to neuron-specific enolase.

Keywords: Carbon monoxide poisoning, Matrix metalloproteinase 9, Hypoxic cell damage, Tau protein, Acute carbon monoxide, Patients.

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1. INTRODUCTION

Acute Carbon monoxide (CO) poisoning is one of the leading poisonings that can result in death due to its early and late effects [1]. The duration of exposure, the amount of CO in the environment, the amount of inhaled air and the health status of the person determine the degree of acute CO poisoning [2, 3]. The bonding of CO with proteins and enzymes such as hemoglobin, myoglobin, and cytochrome oxidase causes toxic effects [4]. Clinical findings vary according to the systems involved and depending on the degree of intoxication, it may lead to a different clinical presentation ranging from nonspecific appearance to coma [5, 6]. Since the brain is the most sensitive organ to hypoxia, the degree of brain involvement often determines the severity of the clinical

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presentation. The diagnosis is made with high levels of carboxyhemoglobin (COHb); however, the COHb level is not sufficient to show the severity of the clinical presentation at the first admission [5, 7, 8]. Therefore, other tests were needed to show the degree of clinical severity of CO poisoning.

S100 calcium-binding protein B (S100B) is primarily produced by astrocytes and has autocrine and paracrine effects on glia cells, neurons and microglia [9]. The significantly higher incidence of S100B in cerebral ischemia suggested that it may indicate the degree of brain involvement in patients with CO poisoning [10 - 16]. Studies conducted in humans have shown that neuron-specific enolase (NSE) levels were increased in various central nervous system (CNS) injuries and diseases (stroke, traumatic brain injury, multiple sclerosis, Alzheimer's disease, and epileptic seizures) [17]. Tau protein is found in the microtubule structure of axons and is released into the cerebrospinal fluid (CSF) in degenerative diseases of the CNS [18]. It is known that Tau protein levels increase due to ischemia [19]. The mode of release of matrix metalloproteinase-9 (MMP-9) has not been fully demonstrated but it has been found to be higher in stroke patients admitted to the emergency department (ED) compared to healthy individuals [20, 21].

It has been shown that S100 and Tau protein increased in patients with CO poisoning (especially in unconscious patients), but Tau protein is more sensitive in showing the severity of intoxication [16]. NSE and S100 levels were observed to be higher in the patients with CO poisoning than in control groups and higher in patients with unconsciousness than in conscious patients [22]. On the other hand, there are not enough studies examining MMP-9 levels in patients with CO poisoning.

The objective of the present study was to investigate the relationship between the level of S100B, NSE, MMP-9, and tau protein and the severity of CO poisoning in the early period.

2. MATERIALS AND METHODS

The study was conducted in the Emergency Medicine and Biochemistry Departments of tertiary hospitals in Gaziantep, Turkey. The Ethics Committee approval was obtained from the local Ethic Committee (Date: 14.09.2015 decision no: 2015/256). Approximately annually 150,000 patients admitted to the adult ED where the study was conducted.

2.1. Inclusion Criteria in the Study

Between November 2015 and March 2016, 34 patients presented with CO poisoning.

Applicant in the first 24 hours of intoxication;

Patients with first transcutaneous carboxyhemoglobin (COHb) level> 5% (10% in smokers) were included in the study.

2.2. Exclusion Criteria from the Study

Do not meet the inclusion criteria;

Not wanting to participate in the study (relatives of unconscious patients).

With a past cerebrovascular disease.

Having a history of previous intracranial bleeding.

Pre-existing nervous system diseases.

Pregnancy.

Having a history of renal failure.

Patients who were exposed (or suspected) to another additional intoxication factor at admission were excluded from the study.

2.3. Collection of Data

2.3.1. Initial Assessment of Patients

Detailed anamnesis and physical examinations of all patients with suspected CO poisoning were performed. The patients' age, gender, time to arrive at the ED (the time from exposure to emergency service), and smoking status were recorded.SpO2 and COHb levels were measured transcutaneously from the fingertip at the first admission. COHb level measurement was made using a signal capture CO-pulse oximeter (Masimo's SET Rainbow, Masimo's Co, USA).COHb levels were confirmed by arterial blood gas analysis (ABG) analysis in all patients.

The patients were divided into two groups as mild and moderate-severe, according to their Glasgow coma scores (GCS) [Mild (14–15); Moderate (9–13) and Severe (3–8)] [23].

Thirty-seven patients who were admitted to the ED were included in the study. However, 3 of these were excluded because no results were obtained in their serum. The control group was composed of 16 healthy and non-smoking volunteers. The volunteers were selected randomly from the hospital staff.

2.3.2. Collection of Blood Samples

From all patients, 8 ml of venous blood was taken from the antecubital area at the first hour of admission and 3rd hour of the treatment. Blood samples taken from patients and volunteers were taken into gel serum tubes. The samples were centrifuged at 4000 rpm for 10 minutes. Then the serum portion was taken and placed in labeled Eppendorf and stored at -80 ^{o}C until the time of use. Samples were taken out and brought to room temperature before the analysis. HNSE (DiaMetra, Italy), Human Mapt (Elabscience, China), MMP-9 (Yehua, China) and S100B (DiaMetra, China) levels in serum samples were measured using the ELISA (Enzyme Linked Immunosorbent Assay) method.

2.3.3. Estimation of S100B, NSE, Tau Proteinand MMP-9

2.3.3.1. S100B Estimation

Serum samples and ELISA reagents were used at room temperature. 50µL of the standards (4000, 1600, 280, 140 and 80 ng / mL) were added to the wells. 50 µL of the samples were added to the well. 50 µL sample buffer was added to the standard and sample wells and incubated for 2 hours at room temperature. After the incubation was completed, unbound material was removed by washing the wells with a washing

solution. 100 µL of diluted conjugate was added to the wells and incubated at room temperature for 60 minutes.After the incubation was completed, unbound material was removed by washing the wells with a washing solution. 100 µL of TMB substrate was added to the wells, and incubated at room temperature for 30 minutes in the dark, and 100 µL of stop solution was added and read at 450 nm with an ELISA reader (Biotek Instruments, USA) [24].

2.3.3.2. NSE Estimation

Serum samples and ELISA reagents were used at room temperature. 25µL of the standards (100, 50, 20, 4 and 0 ng / mL) were added to the wells. Measurements were made according to the protocol mentioned above (Biotek Instruments, USA) [24].

2.3.3.3. Tau Protein Estimation

Serum samples and ELISA reagents were used at room temperature. 100 µL of samples and standards (500; 125; 62.5; 31.25; 15.6; 7.8 and 0pg / mL) were added to the wells. Measurements were made according to the protocol mentioned above (Biotek Instruments, USA) [24].

2.3.3.4. MMP-9 Estimation

Serum samples and ELISA reagents were allowed to come to room temperature. 50 µL of the standards (4800; 2400; 1200; 600 and 300 ng / L) was added to the wells. Measurements were made according to the protocol mentioned above (Biotek Instruments, USA) [24].

2.4. Statistical Analysis

Statistical analysis was conducted using SPSS 18.0 program (SPSS for Windows, 18.0 SPSS Inc, USA). Kolmogorov-Smirnov test was used in the distribution analysis of the data. Mann Whitney's test was used to compare parameters between patient and control groups. Wilcoxon test was used to compare parameters within the same group. All data were expressed as mean ± standard deviation, and $p < 0.05$ was considered statistically significant.

3. RESULTS

Thirty-four patients with CO poisoning and 16 people as the control group were included in the study. 35.3% (n = 12) of the patients with CO poisoning were male and the mean age was 36.8 ± 13.4 (19-80). The mean admission time to the emergency department with CO poisoning was 107.2 ± 117.19 minutes. CO poisoning in all patients occurred due to the use of coal stoves. The average transcutaneous COHb levels of the patients measured at the first admission were 27.2 ± 7.5% and their oxygen saturation was 96.2 ± 5.1%. 76.5% (n = 26) of the patients were non-smokers, and 28 (82.4%) patients were categorized as mild (Table **1**).

There was a statistically significant increase in serum NSE and Tau protein levels in the patient group at 0 and 3rd hour as compared to control. Although the S100B protein and MMP-9 levels were insignificantly higher in the patient group than control (Table **2**).

At 0 and 3 hours, serum S100B protein, NSE and MMP-9 values were statistically insignificantly higher in those with moderate-severe patients, was found. Tau protein at 0 and 3 hours levels were found to be statistically significantly higher in moderate-severe patients as compared to control (Table **2**).

When the control group and mild patients were compared; The serum S100B protein and MMP-9 values at 0 and 3 hours were statistically insignificantly higher in mild patients, Tau protein and NSE at 0 and 3 hour levels were found to be statistically significantly higher in mild patients (Table **2**).

When mild patients and moderate-severe patients were compared, no significant difference was found between the S100B, NSE, MMP-9 and Tau protein levels measured at 0 and 3 hours ($p > 0.05$).

Since there is no hyperbaric oxygen therapy unit in this center, all patients were oxygenated by reservoir oxygen masks. Mortality was not observed in any patient. All patients were discharged from ED without neurological sequelae.

Table 1. Descriptive data of the groups.

Parameter	**Total Patient Group (n=34; 100.0%)**	**Control Group (n=16; 100.0%)**
Age (years) mean ± SD (min-max)	36.8±13.4 (19-80)	30.4±6.6 (21-41)
Gender **n (%)** Male Female	 12 (35.3%) 22 (64.7%)	 5 (31.3%) 11 (68.7%)
Emergency arrival time (minutes) mean ± SD	107.2±117.19	-
Transcutaneous CO level at first admission (COHb%)	27.2±7.5%	1±1%
Transcutaneous SpO2 level at first admission (%)	96.2±5.1%	96.1±1.8%
Smoking **n (%)** Yes No	 n=8 (23.5%) n=26 (76.5%)	 n=0 (0%) n=16 (100%)
Glasgow coma score Mild Moderate-severe	 n=28 (82.4%) n=6 (17.6%)	-

Note: min: minimum; max: maximum; SD: standard deviation; COHb: Carboxyhemoglobin; SpO2: Peripheral oxygen saturation.

Table 2. Comparative data of the control group and patient groups.

Parametre	Control Group (n=16; 100.0%)	Total Patient Group (n=34; 100.0%)	Mild Patients (n=28; 82.4%)	Moderate-severe Patients (n=6; 17.6%)
S100b 0. Hour pg/ml	1022.6±978.1	1371.5±784.8 P1=0,205	1320.3±763 P2=0,306	1610.4±915 P3=0,161
S100b 3rd Hour pg/ml	1022.6±978.1	1165.1±654.6 P1=0,328	1165.2±645 P2=0,367	1164.7±760 P3=0,461
NSE 0. Hour ng/ml	12.4±6.9	27.7±33.8 P1=0,001*	29.7±36.8 P2=0,001*	18±7.4 P3=0,077
NSE 3rd Hour ng/ml	12.4±6.9	18.9±12.3 P1=0,023*	20.3±13 P2=0,007*	12±4.7 P3=0,883
Tau Protein 0. Hour pg/ml;	13.6±7.9	41.8±36.2 P1=0,000*	41.9±37.5 P2=0,000*	41.5±32 P3=0,022*
Tau Protein 3rd Hour pg/ml;	13.6±7.9	37.5±31.6 P1=0,008*	35.1±30.7 P2=0,019*	49±36 P3=0,018*
MMP-9 0. Hour ng/l	1714.9±1465.2	2313.7±3123.7 P1=0,270	2368.3±3143.7 P2=0,341	2058.6±3307.4 P3=0,302
MMP-9 3rd Hour ng/l	1714.9±1465.2	2226.2±2809 P1=0,492	2283.1±2772.7 P2=0,661	1960.6±3234.5 P3=0,269

Note: P values were obtained by the Mann-Whitney Test. * Significant p <0.05. P1: Control group versus total patient group, P2: Control group versus Mild patients group, P3: Control group versus Moderate-severepatients group.

4. DISCUSSION

The severity of the case and mortality in patients with CO poisoning is to study the affect on the brain which is the most sensitive organ in the human body. Toxic brain damage often develops due to tissue hypoxia in the patients with CO poisoning. Neurological symptoms occur in patients with brain damage and Glasgow coma scale (GCS) decreases in patients with more advanced brain damage. Four of the parameters were shown to be elevated in ischemic brain injury or traumatic brain injury.

Xue and coworkers (2017) conducted a study with rats, MMP-9 levels were increased significantly after exposure to CO and were inhibited by hyperbaric oxygen (HBO2) treatment [25]. It has been found that MMP-9's release, ischemia increases and contributes to the developing edema by increasing vascular permeability [26]. An increase in MMP-9 levels was found in stroke patients (both ischemic and hemorrhagic) admitted to the emergency department compared to healthy individuals, and this increase is thought to occur in a short period (within hours) [20, 21]. Acute MMP-9 increases were associated with infarct size, hemorrhage, transformation complications, and poor neurological outcomes [20, 27, 28]. Zhong and coworkers (2017) followed up 3,186 acute ischemic stroke cases; they defined high serum MMP-9 levels as a factor that increases mortality [29]. Abdelnaseer and coworkers (2017) followed 30 acute ischemic stroke cases; it has been shown that serum MMP-9 levels are higher in cases of ischemic stroke (compared to the control group), and that it is higher in cases with poor neurological cases (compared with patients with good neurological case) [30]. Statistically insignificant difference in MMP-9 values between the patient group and the control group (p> 0.05) was observed. In addition, there was an insignificant difference between mild patients and moderate-severe patients (p> 0.05). No relationship between CO poisoning and MMP-9 was observed. MMP-9 levels in healthy individuals were reported in the range of 11.4–64 ng/ml [31, 32]. Abdelnaseer *et al.*.(2017) reported that the serum MMP-9 level of the control group was 691.8 ± 232.37 ng/ml (30) and Zhong *et al.*. (2017) reported that the median MMP-9 level of 3186 patients with acute ischemic stroke was 671.8 ng / mL [29]. In the study of Che and coworkers (2019with 558 acute ischemic stroke cases, the median serum MMP-9 level of the patients was 567.6 ng / mL [33]. Mean serum levels of MMP-9 in both the control group and the patient group was found to be considerably higher than reported values. The fact that CO poisoning is most common in the winter months and the waste products of fossil fuels used for heating in these months [air pollution (such as particulate matter, NO_2, CO, CO_2)] are epidemiological factors may be affecting both the control group and the patient group.

Discussion on MMP-9 and CO poisoning should be rewritten, as it is very unsystematic.

S100B release from astrocytes occurs under metabolic stress such as the absence of oxygen and glucose [9, 34]. S100B nanomolar levels, which act in a dose-dependent manner, stimulate neuronal growth and increase neuron survival, at micromolar levels, the opposite effects occur and even stimulate neuronal apoptosis [35, 36]. S100B is an important factor in neural development, differentiation and repair of the brain, and additional cell damage caused by increases in extracellular concentration after brain damage also plays a role in the pathophysiology of neurodegenerative formation [37]. Many studies have shown that S100B secretion increases up to 48 hours after the onset of symptoms, and the peak concentration is within the first 24 hours after cerebral infarction [38 - 40]. Relationship between the severity of CO poisoning and S100B values was reported. While the studies of Rasmussen (2004), Akelma (2013) and Gawlikowski (2014) showed that S100B values did not increase significantly in patients with CO poisoning, but it was found to be significantly higher in the studies of Brvar (2003), Çakır (2010) and Yardan (2009) [11 - 16, 22]. In the study conducted by Akdemir and coworkers, S100B increased in patients with CO poisoning, but no significant difference was found in those with confusion

compared to those without confusion [14]. S100β has been shown to be a very valuable parameter for early evaluation and prognosis prediction in CO poisoning [41]. In the present study, S100B values were not found to be statistically significant between the patient group and the control group ($p > 0.05$), and there was no significant difference between mild patients and moderate-severe patients ($p > 0.05$). Based on these data, no possible relationship between S100B and CO poisoning may be established during the early period of CO poisoning.

When cultured neurons were exposed to cytotoxic agents *in vitro*, NSE released from neurons and increased NSE levels may be a good marker for quantifying neuron cell death [17]. It has been shown that NSE levels in CSF were increased in various CNS injuries and diseases (stroke, traumatic brain injury, multiple sclerosis, Alzheimer's disease and epileptic seizures) in humans [17]. Previous studies indicate that there is no correlation between NSE content and CO poisoning as compared to control [11,12 Yardan and Akelma reported higher NSE levels in patients who have developed confusion [13, 22]. Akdemir and coworkers (2013) reported significantly higher CO poisoning as compared to the control group, insignificant difference was found between those with and without confusion [14]. In this study, the NSE level was higher in patients with CO poisoning. Looking at the subgroups, the NSE level was higher in mild patients than in the control group. However, no significant difference was observed between the moderate-severe patients and the control group. This may be related to the smaller number of moderate-severe patients.

Tau protein contributes to the assembly and maintenance of the structure of microtubules in axons [41]. As a result of the loss of axonal microtubules, intracellular microtubule binding proteins such as Tau are released and pass into the extracellular space, so the CSF levels of Tau reflect axonal damage due to head trauma, Alzheimer's disease, and meningitis [42]. In a study conducted on patients presenting with acute stroke, it has been shown that total Tau protein level in CSF increases continuously from the first day and returns to normal levels from the third or fifth month [19]. Kılıçaslan and coworkers (2012) followed 78 patients of CO poisoning; Tau protein levels were higher in patients with confusion [43]. Gawlikowski and coworkers (2014), analyzed 27 carbon monoxide poisoned patients and found that Tau protein levels were higher in the patient group (with or without confusion) compared to the control group [16]. In the present study, Tau protein was found to be statistically significantly higher in the CO-exposed patient group as compared to the control group ($p < 0.05$), but there was no significant difference between mild patients and moderate-severe patients ($p > 0.05$).

This study showed that Tau protein levels increase in CO intoxication. However, high Tau protein levels are not associated with the severity of the clinical presentation of patients.

5. LIMITATIONS

Seasonal conditions and air pollution also affect the parameters examined in the control group and CO poisoning patients. The exposure time of the patients to carbon monoxide is not clearly known.

CONCLUSION

There was no relationship between CO poisoning and MMP-9 and S100B protein levels. NSE and Tau protein was higher in the patient group than in the control group. Tau protein can be a more useful marker as compared to NSE.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics committee approval was obtained from Gaziantep University (Date: 14.09.2015 decision no: 2015/256).

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

Informed consent was obtained from each participant.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

Submitted work is original and has not been published elsewhere in any language. Raw data are available for the corresponding author [M.B] on request.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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