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Research Article

Does Hypoxia-Inducible Factor-1A Levels Contribute to the Diagnosis and Follow-Up of Carbon Monoxide Poisoning?

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Abstract

Objectives: This study aimed to evaluate the levels of HIF-1α (Hypoxia-Induced Factor) in acute Carbonmonoxide poisoning (COP) at admission and after the treatment.

Methods: The study was conducted prospectively and cross-sectionally in the adult Emergency Department of our hospitalbetween 01.01.2018 and 30.06.2018.

Results: This study included 42 patients admitted to the emergency department with suspected COP. When the cases were grouped according to carboxyhemoglobin (COHb) level, the levels of 38.1% (n=16) and 61.5% (n=26) of the patients were found to be moderate and severe, respectively. There were no mild cases among our cases. After the treatment, HIF-1α, COHb, mean platelet volume (MPV), lymphocyte, lactate, pH and base deficit values were statistically significantly lower than the pre-treatment values(p value<0.0001, <0.0001, <0.0001, 0.039, <0.0001, 0.032, 0.01, respectively). A positive correlation was found between COHb level and white blood cell (WBC), neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), pH, HIF-1α and lactate levels. There was a statistical significance only at pH value (p=0.001, r=0.474).

Conclusion: HIF-1α increases significantly in parallel withCarbonmonoxide(CO) exposure and these high levels are positively correlated with COHb concentrations. Based on this data, COHb concentrations are still the best biomarkers in the diagnosis and follow-up of COP.

Keywords: Carbonmonoxide poisoning, HIF-1α, COHb, Emergency department, Toxicology

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CO is a colorless, tasteless, odorless, lighter-than-air, non-irritating toxic gas. COP is one of the common types of poisoning in the world.Approximately 50000 patients are admitted toemergency departmentswith COPin a yearin the USA.[1,2] The incidence of COP increases due to the use of carbon-based fuels, and the use of flue-free stoves, barbecues and water heaters in small areas with insufficient ventilation is the most important cause of poisoning in our country.[3,4] CO leads to various temporary and permanent effects on human bodydepending on the time of exposure and the effects of treatment.[5] Heart and brain are the most responsive organs to COP due to their high metabolic rates, and neuropsychiatric.[6] Classical complaints in acute intoxications are headache, dizziness, nausea, vomiting, dyspnea, and chest pain. Findings range from minimal symptoms to nonresponsiveness, hypotension, severe acidemia and/or acute respiratory failure.[7]

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Although COHb levels in blood gases are used as diagnostic tests, a low correlationwas shown amongCOHb levels and clinical studies.[1,2] Nowadays, the diagnosis of COP is based on past and physical examination consistent with high COHb levels.[8] >10% of COHb without clinical symptoms and signs is mild poisoning; >10% of COHb with mild symptoms and signs (headache, lethargy, fatigue) is moderate poisoning; >20-25% of COHb with loss of consciousness, confusion or cardiac ischemia is severe poisoning. [9] High flow oxygen (NBO) with mask is the first and main treatment approach to patients who are suspected or diagnosed in the emergency department (ED), and treatment should be continued until COHb levels of patients reach normal levels (≤3%) and their symptoms resolve (at least 6 hours).[1]

COP is discussed in two parts.According to the hypoxia theorem, CO particlereduces the oxygen carrying capacity of the cells by binding to hemoglobin 230-270 times more than oxygen, resulting in hypoxia in all tissues in the body. [2,10] According the cellular theorem, CO inhibits the mitochondrial transport enzyme system in cells.[2,11] Polymorphonuclear leukocytes increase, causing lipid peroxidation in brain. Lipid peroxidation isaccountable for the belated neurological effects of COP.[10,12] Oxidative stress in COP plays a role in hypoxic ischemic brain injury, and COP increases the production of reactive oxygen types.[2,5]

Hypoxia-inducible factor(HIF): When tissues are submitted to hypoxia, the amount of oxygen in tissues reduces. Decreased oxygen levels warn post-translational modification of proteins and cell metabolism, which starts gene transcription. HIFs are regulatory molecules in oxygen hemostasis.[13] HIF is heterodimericconsisting of two main subunits, alpha&beta, and it has three forms, HIF-1, HIF-2, HIF-3. The activity of β subunit is not affected by hypoxia, whereas the α subunit is a highly regulated and active subunit (14,15).The most known and examined forms are HIF-1α&HIF-2α. HIF-1α is a very important mediator of cellular and molecular responses to hypoxia.[16] HIF-1α is stated in whole-core cells and provides rapid response to hypoxia.[17] Hypoxia reduces usual hydroxylation of HIF by limiting proteolytic degradation. The factors like erythropoietin, glycolytic enzymes, vascular endothelial growth factor and adrenomedullin modulated by HIF-1α are involved in the modulation of angiogenesis, erythropoiesis, glycolysis,oxygen&energy supply.[16]

The importance of biochemical markers such as ischemia-modified albumin (IMA) and HIF-2α as an alternative to COHb, a traditional marker in the COP due to poor correlation amongCOHb levels and clinical picture in the patients with COP, has become an increasing research topic recently.[2,3]

This study intendedto evaluate the levels of HIF-1α, a biochemical marker considered to play a role in acute hypoxia, at admission and after the treatment and to compare the levels of COHb, blood gas and hemogram parameters in patients admitted to the ED due to acute COP.

Methods

Study Design & Setting

The study was conducted prospectively and cross-sectionally in the adult ED of our hospitalbetween 01.01.2018 and 30.06.2018. 53312 patients were admitted to the ED and 263 cases were intoxicationpatients. A total of 58 of patients with poisoning had COP, and 42 patients who met theinclusion criteria were examined. Our study was reviewed and approved by the Clinical Research Ethics Review Committee of Kahramanmaraş Sütçü İmam University Faculty of Medicine with the approval number of 2018/01-26 and the date 03.01.2018.

Selection of the Subjects

The study included 42 patients aged 18 years and older who were admitted to the ED with suspected COP, had COHb value ≥10% in case of venous blood gas, and had isolated COP. Three patients with fire-associated smoke intoxication were excluded because they could be exposed to other toxic gases (cyanide, etc.) other than CO.

Study Protocol, Measurements, Data Collection

The diagnosis of COP in patients admitted to the EDwith suspected COP was based on patients' history and the detection of COHb levels higher than normal in venous blood gas in ED.[8] During admission, venous blood wascollected from all patients, who were suspected to have COP and didn't receive O_2treatment, for the examinations like blood gas, complete blood count (CBC) and cardiac markers. Venous blood samples were collectedfrom these patients for HIF-1α measurement in non-anticoagulant yellow-cap tubes. 12-lead electrocardiography (ECG) was performed for all patients during initial evaluation. Patients with a final diagnosis of COP were monitored and their NBO treatment was started. At the sixth hour after O_2treatment, venous blood samples were collected again from the patients to compare the changes in CBC, blood gas and HIF-1α parameters. Routine blood samples were studied for 20 minutes in the emergency laboratory. Complete blood counts were analyzed using Sysmex XT-1800 automatic hematology device (Sysmex, Kobe/Japan). Among hemogram parameters, WBC (leukocyte), platelet, neutrophil and lymphocyte counts and mean platelet volume (MPV) were used. Neutrophil Lymphocyte Ratio (NLR), Platelet Lymphocyte

Ratio (PLR) were calculated. Venous blood gas parameters were measured by Radiometer ABL800 (Radiometer, Copenhagen/Denmark). Among blood gas parameters, pH, pO_2, pCO_2, O_2 saturation, COHb, lactate and base deficit parameters were used. Cardiac enzyme (Troponin-I) level was measured by Radiometer AQT-90 (Radiometer, Copenhagen/Denmark).

For the measurement of HIF-1α, blood samples taken in yellow-lid tubes without anticoagulant were centrifuged for 10 minutes at 4000 rpm after they were expected to coagulate at room temperature, and serum was obtained. Serum samples were kept at (-)80oC until the working day. Serum samples obtained for HIF-1α measurement were brought to room temperature on the working day. Serum HIF-1α levels were determined by applying commercial ELISA kit procedures (SEA798Hu; Cloud-Clone Corp., Houston/USA).As a result of clinical follow-ups, patients whose CO levels in blood gas returned to normal (≤3%) and those with no clinical symptoms were planned to be discharged. The changes in these patients' parameters during their admission to the adult ED and at the sixth hour of follow-up were examined. Participants were informed about the study andfilled out the informed consent forms. Normal range of markers is presented in Table 1.

Statistical Analysis

SPSS22 package program was used for the statistical evaluation of the data (SPSS Inc, Chicago-Illinois/USA). Continuous data were summarized as means and standard deviations, and categorical data were summarized as numbers and percentages. Kolmogorov-Smirnov test and histogram evaluations revealed normally distributed variables. Paired Sample t test was used to compare the mean values of HIF-1a and other biomarkers measured before and at the sixth hour of treatment. Pearson correlation test was used to determine the correlationbetween two continuous variables. The statistical significance level was considered to bep<0.05.

Table 1. Markers; normal values

Markers	Normal range
HIF-1α (ng/mL)	0.23-15.0
Number of leukocytes (10^9/L)	3.4-8.9
Platelet (10^9/L)	150-400
Neutrophil count (10^9/L)	1.5-5
Lymphocyte count (10^9/L)	1.1-3.17
MPV (fL)	9.2-12.2
NLR	
PLR	
Lactate (mmol/L)	0.5-1.6
Ph	7.35-7.45
PCO_2 (mmHg)	32-48
PO_2 (mmHg)	83-108
Base deficit (mmol/L)	(-)3-(+)3
O_2Saturation (%)	95-99
COHb (%)	0.5-1.5

Results

Of 42 patients, 38.1% were male (n=16) and 61.9% were female (n=26). Patients' mean age was 41.1±11.8 years (minimum-maximum: 24-66 years).

When the patients exposed to COP for different reasons were examined,stove poisoning was observed to be the most important reason by 85.7% (n=36). Other reasons were water heater by 4.8%, barbecue by 4.8% and central heating boiler by 4.8%.

When the symptoms of patients were examined, nausea was the most common complaint by 52.4% (n=22). Other symptoms were headache by 47.6%, dizziness by 47.6%, vomiting by 19%, syncope by 14.3%, clouding of consciousness by 4.8%, and drowsiness by 4.8%.

When patients' Glasgow Coma Scores (GCS) during admission were examined,it was GCS=11 in two cases, GCS=14 in six cases, and GCS=15 in 34 cases (15).

The mean systolic blood pressure (SBP) measured before the treatment was 120.4±13.5 mmHg (minimum-maximum: 100-152mmHg), the mean diastolic blood pressure (DBP) was 65.4±8.9 mmHg (minimum-maximum:50-86mmHg), and the pulse was 89.5±13.0 beats/min (minimum-maximum: 60-112beats/min). ECG was performed in cases and troponin values were examined. As a result of ECG evaluation, more than half of the cases (57.1%) were in normal sinus rhythm. Sinus tachycardia was seen in 28.6% of cases, and anterior pointed T sign associated with ischemia was present in 14.3% of cases. Patients' troponin levels were normal.

When the cases were grouped according to COHb level, the levels of 38.1% (n=16) and 61.5% (n=26) of the patients were found to be moderate and severe, respectively. There were no mild cases among our cases.

After the treatment, HIF-1α, COHb, MPV, lymphocyte, lactate, pH and base deficit values were statistically significantly lower than the pre-treatment values. There was a statistically significant increase in pCO_2, pO_2 and O_2saturation values after the treatment compared to the pre-treatment values. The data on CBC parameters, blood gas parameters and HIF-1α values examined before treatment and six hours after treatment are presented in Table 2.

Table 2. Evaluation of markers of the sixth hour of treatment and pre-treatment of patients with COP.

Markers	Pre-treatment Mean±SD	Sixth hour of treatment Mean±SD	p*
HIF-1α (ng/mL)	0.218±0.13	0.081±0.04	<0.0001
Number of leukocytes (10_9/L)	8.7±3.1	8.4±2.3	0.264
Platelet (10_9/L)	246.9±61.5	248.6±58.3	0.499
Neutrophil count (10_9/L)	5.6±3.0	5.9±2.2	0.431
Lymphocyte count (10_9/L)	2.2±0.8	2.0±0.7	0.039
MPV (fL)	10.3±0.7	10.1±0.8	<0.0001
NLR	3.1±2.8	3.3±1.5	0.625
PLR	124.2±50.6	135.6±37.6	0.083
Lactate (mmol/L)	2.8±2.1	1.5±1.0	<0.0001
Ph	7.40±0.06	7.38±0.03	0.032
PCO_2 (mmHg)	36.5±5.9	39.8±4.6	<0.0001
PO_2 (mmHg)	23.0±5.1	42.2±3.12	<0.0001
Base deficit (mmol/L)	(-)2.0±1.5	(-)1.2±2.1	0.01
O_2Saturation (%)	54.1±9.0	74.3±15.7	<0.0001
COHb (%)	20.5±6.4	6.1±3.4	<0.0001

*Paired Sample t-test was used to compare markers; HIF-1α: Hypoxia-inducible factor-1α,WBC: White blood cells, MPV: Mean platelet volume, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, pCO2: Carbondioxide pressure, pO2: Blood oxygen pressure p<0.05 value was considered statistically significant.

A positive correlationwas found between COHb level and WBC, NLR, PLR, pH, HIF-1α, and lactate levels before the treatment. There was a statistical significance only at pH value. There was a negative correlationbetween platelet count, PCO_2, PO_2 and base deficit, which was statistically significant in platelet count, PCO_2 and PO_2 (Table 3).

A positive correlation was found betweenCOHb level and NLR, pH at the sixth hour of treatment. A negative correlation was found between COHb level and platelet count. A positive correlation was found between HIF-1α and PO_2. Correlation analysis of six hours of treatment datais presented in Table 4.

Discussion

CO is a toxic gas. CO's tastelessness, colorlessness, and odorlessnessincreasethe danger. Every year in our country, especially in autumn and winter, news about COP from stove or water heater is seen in media and there are dramas resulting in the deaths of whole family. The frequency of COP in the world varies by countries depending on climatic and socioeconomic characteristics. The rate of COP in our country is 0.014% per year,[18] however, it is 0.016% in the USA.[8] In our study, it was found to be 0.108%. We believe that six-month period studies and more frequent cases in winter and spring are the main reasons of this rate.

In our country, the usage of stoves, barbecues and water heaters is the most important cause of COP.[3] The literature has shown that poisonings due to stoves are the most common cause of poisoning.[3,4,19] The results of our study supported the literature. It is considered to be due to reverse winds in our region, which are very strong and lead to backlash in winter. As a solution to it, local authorities should inform community about poisoning during windy periods.

Whole body systems, especially central nervous system, are affected in COP.[1] Clinical findings in sick people vary from minimal symptoms to unresponsiveness, hypotension, severe academia or acute respiratory failure. Classical findings in acute intoxications usually include headache, dizziness, nausea, vomiting, dyspnea and chest pain.[7] In the study of Ciftci et al., the frequent symptoms due to CO poisoning are headaches, dizziness, weakness, nausea, vomiting, mental state changes, chest pain, shortness of breath, and loss of consciousness.[20] In the study of Altıntop et al., headache(46.4%) was the most prevalent complaint, followed by nausea with vomiting(42.9%), asthenia and weakness(41.1%).[3] In this study, the most prevalent complaintwas nausea, and headache and dizziness were the other common complaints.

COP is a significant cause ofmortality and morbidity. Today, COHb level measured after exposure to CO is the gold standard in diagnosing COP.[1] The severity of intoxication is divided into 3 groups as mild, moderate, severe, based on the measured COHb levels.[9] In a recent study in Turkey, 35 patients with COHb levels above10% were recruited, but these patients were not classified among themselves.[3] In

Table 3. Evaluation of the correlation between COHB and HIF-1α and other markers before treatment.

	COHb (n:42)	HIF-1α (n=42)
WBC (10^9/L)	r=0.036	
	p=0.823	r=-0.132
	p=0.404	
NLR	r=0.110	
	p=0.487	r=-0.117
	p=0.462	
PLR	r =-0.117	
	p=0.462	r=0.006
	p=0.972	
Platelet (10^9/L)	r=-0.440	
	p=0.004	r=0.005
	p=0.977	
pH	r=0.474	
	p=0.001	r=0.142
	p=0.371	
pCO_2 (mmHg)	r=-0.443	
	p=0.003	r=-0.047
	p=0.766	
HIF-1α (ng/ml)	r=0.108	
	p=0.497	r=1
Lactate (mmol/L)	r=0.172	
	p=0.275	r=-0.48
	p=0.765	
Base deficit (mmol/L)	r=-0.212	
	p=0.177	r=0.089
	p=0.574	
pO_2 (mmHg)	r=-0.515	
	p<0.0001	r=0.005
	p=0.976	

Pearson correlation coefficient was used to compare the markers; WBC: White blood cells, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, pCO2: Carbondioxidepressure, HIF-1α: Hypoxia-inducible factor-1α, pO2: Blood oxygen pressure. p<0.05 value was considered statistically significant.

Table 4. Evaluation of the correlation between COHB and HIF-1α and other markers six hours of treatment.

	COHb (n:42)	HIF-1α (n=42)
WBC (10^9/L)	r=0.163	
	p=0.301	r=-0.241
	p=0.125	
NLR	r=0.367	
	p=0.017	r=0.050
	p=0.754	
PLR	r=-0.003	
	p=0.983	r=0.324
	p=0.036	
Platelet (10^9/L)	r=-0.336	
	p=0.029	r=0.042
	p=0.791	
pH	r=0.618	
	p<0.0001	r=-0.073
	p=0.646	
pCO_2 (mmHg)	r=-0.282	
	p=0.071	r=-0.045
	p=0.776	
HIF-1α (ng/ml)	r=-0.241	
	p=0.125	r=1
	p=	
Lactate (mmol/L)	r=0.119	
	p=0.451	r=-0.090
	p=0.573	
Base deficit (mmol/L)	r=0.144	
	p=0.364	r=-0.031
	p=0.845	
pO_2 (mmHg)	r=0.165	
	p=0.297	r=0.389
	p=0.011	

Pearson correlation coefficient was used to compare the markers. WBC: White blood cells, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, pCO2: Carbondioxidepressure, HIF-1α: Hypoxia-inducible factor-1α, pO2: Blood oxygen pressure. p<0.05 value was considered statistically significant.

our study, most of the patients were in the severe poisoning class and no patients were in the mild poisoning class.

Although COHb levels in blood gases have been used as diagnostic tests, the weakness of the correlationbetween COHb levels and clinical trials is still a matter of debate.[1,2,21] Even in patients with high COHb levels, 20-30% of the clinic picture is shown to be asymptomatic.[6] The time until the measurement of COHb level, the concentration of the exposed CO, exposure time, baseline status of exposed patient, individual sensitivity, and the amount of treatment O_2 during treatment are thought to play a role in this case.[2,22] Thus, alternative biochemical markers to COHb, a traditional marker in the diagnosis of COP and prognosis, have become an increasingly important research topic recently. Giuseppe et al.[11] studied fatty acid binding protein (FABP), and Yardan et al.[23] studied heart-type fatty acid binding protein (H-FABP) in determining and following cardiac injury in COP patients and concluded that these markers can be used as an alternative to troponin. Türedi et al. found that IMA concentration in rats increased significantly at the 1st and 6th hours of exposure to CO.[2] In a study examining serum HIF-2α levels in COP patients, there was a positive correlationbetweenCOHb levels & HIF-2α levels during admission (p=0.005, r=0.464), and it was stated that HIF-2α can be used even in the follow-up of COP patients at 12th and 24th hours.[3] Choi et al. have shown that CO stimu-

lates the generation of vascular endothelial growth-factor (VEGF), a significant angiogenic factor, with increasing HIF-1α protein level after hypoxia.[24] Bani et al. showed that CO-induced O_2 deprivation was a strong stimulus against hypoxic stress responses regulated by cerebral HIF-1α, which caused an increase in Adrenomeduline (AMD) and VEGF especially at the 12th hour ($p<0.01$).[25] HIF-1α is a significant mediator of molecular andcellecular reaction to hypoxia.[16] HIF-1α is stated in all-core cells and provides rapid response to hypoxia.[17] The factors like erythropoietin, glycolytic enzymes, VEGF and AMD modulated by HIF-1α are involved in the modulation of glycolysis, energy supply, oxygen, angiogenesis and erythropoiesis.[16] After the inhalation of HIF-1α CO, it can be detected in 1-4 hours in serumand reaches its peak after 4 hours.[12,26,27] Similar to literature in our study, pre-treatment HIF-1α levels were high as in COHb levels. HIF-1α and COHb values measured at the sixth hour after the treatment were statistically significantly lower than the pre-treatment values ($p<0.0001$). There was a positive correlation between COHb levels & HIF-1α levels before the treatment, which can be considered as an effect of oxidative stress and hypoxic status due to elevated blood COHb concentration.

Lactate is another molecule associated with ischemic intolerance, which significantly increases in CO exposure as shown in this study ($p<0.0001$). A positive correlationwas found between COHb levels and lactate as in HIF-1α in patients evaluated before the treatment. The study of Altıntop et al. showed that lactate levels increased significantly after exposure to CO ($p=0.017$), supporting our study.[3] Additional studies are needed to reveal the specificity of lactate to hypoxia.

A positive correlation was found between HIF-1α level and WBC, NLR, PLO, pH, COHb and lactate levels. After treatment, HIF-1α, COHb, MPV, lymphocyte, lactate, pH and base deficit values were lower than pretreatment values, and this decrease was statistically significant. Post-treatment pO_2 and O_2 saturation values were statistically significantly higher than pre-treatment values, and HIF-1α levels were found to be low after treatment.

In a study determining myocardial injury in patients with COP, there was positive correlation betweenCOHblevels&NLR during admission.[28] In our study, there was a positive correlation between NLR level and COHb level.

Limitations

We are aware that our data and interpretations are limited by a small sample size. We considered that it was important to share our data to assist clinicians at the bedside.

Conclusion

The most important point in the follow-up and treatment of patients with COP is to determine the presence and grade of ischemic injury. The duration and grade of damage of treatment are very important for prognosis. HIF-1α increases significantly in parallel with CO exposure and these high levels are positively correlated with COHb concentrations. Based on this data, COHb concentrations are still the best biomarkers in the diagnosis and follow-up of COP. Furthermore,HIF-1α can be used as an alternative biomarker to evaluate COP.

Disclosures

Ethics Committee Approval: Ethics committee approval was obtained from Kahramanmaraş Sütçü İmam University Faculty of Medicine Clinical Research Ethics Committee on 03.01.2018 with the decision number 26 of 2018/01 session.

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Conflict of Interest: None declared.

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