ANKARA MEDICAL JOURNAL

Research Article

Ankara Med J, 2021;(3):428-440 // 10.5505/amj.2021.68335

OXIDATIVE STRESS IN PATIENTS WITH CARBON MONOXIDE POISONING

KARBON MONOKSİT ZEHİRLENMESİ OLAN HASTALARDA OKSİDATİF STRES

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Geliş Tarihi (Submitted): 11.04.2021// Kabul Tarihi (Accepted): 15.09.2021

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ANKARA MEDICAL JOURNAL

Öz

Amaç: Oksidatif stres, hücresel savunma mekanizmalarıyla (antioksidanlar) elimine edilenden daha fazla reaktif oksijen türü (ROS) oluşumunu ifade eder. Bu çalışmanın amacı, CO zehirlenmesinde gelişen oksidatif stresi belirlemek, oksidan ve antioksidan parametreleri ölçmek ve normobarik oksijen (NBO9 ve hiperbarik oksijen (HBO) tedavilerinin bu parametreler üzerindeki etkilerini incelemektir.
Materyal ve Metot: Acil servise başvuruda ve oksijen tedavisi sonrası 24. saatin sonunda toplam oksidan durum (TOS) oksidatif stres parametresi, total antioksidan durum (TAS), paraoksonaz (PON), serum paraoksonaz (SPON), arilesteraz (ARES) ve tiol (TTL) seviyeleri, antioksidan kapasite göstergesi olarak ölçüldü.
Bulgular: Hasta grubunda kontrol grubuna göre TAS, TTL ve ARES düzeyleri anlamlı olarak düşük bulundu. Hiperbarik tedavi ve normobarik tedavi alan hastalar arasında oksidatif stres parametrelerinin hem başlangıç hem de 24. saat düzeylerinde farklılık yoktu.
Sonuç: TAS, PON, SPON, ARES ve TTL'de devam eden düşüş, antioksidan kapasitenin henüz değiştirilmemiş olmasından veya reperfüzyon iskemisinin tedaviden kaynaklanmasından kaynaklanıyor olabilir. Çalışmamızın sonuçları CO zehirlenmesi vakalarında oksidatif dengenin antioksidanlara ters döndüğünü desteklemektedir.

Anahtar Kelimeler: Karbon monoksit zehirlenmesi, oksidatif stres, hiperbarik oksijen tedavisi.

Abstract

Objectives: Oxidative stress refers to formation of more reactive oxygen species (ROS) than that are eliminated by cellular defense mechanisms (antioxidants). The aim of this study is to determine oxidative stress developed in CO poisoning, to measure oxidant and antioxidant parameters and to study the effects of the NBO and HBO treatments on these parameters.
Materials and Methods: On admission to emergency department and at the end of 24th hour after the oxygen therapy, total oxidant status (TOS) was measured as an oxidative stress parameter, total antioxidant status (TAS), paraoxonase (PON), serum paraoxonase (SPON), arylesterase (ARES), and thiol (TTL) levels were measured as indicators of antioxidant capacity.
Results: TAS, TTL and ARES levels were found to be significantly lower in the patient group when compared to control group. There were no differences in both inital and 24th hour levels of oxidative stress parameters between the patients who received hyperbaric therapy and normobaric therapy.
Conclusion: Continuing decrease of TAS, PON, SPON, ARES, and TTL may be because the antioxidant capacity has not yet been replaced or reperfusion ischemia is caused by treatment. The results of our study support that oxidative balance turns against antioxidants in cases of CO poisoning.

Keywords: Carbon monoxide poisoning, oxidative stress, hyperbaric oxygen therapy.

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Introduction

Carbon monoxide (CO) is a tasteless, colorless, odorless, and nonirritant gas, which produced by incomplete combustion of carbon-based fuels and other substances. CO is the leading agent causing death due to poisoning.[1]

Early symptoms of CO poisoning are first seen in oxygen-dependent organs such as the brain and heart; the symptoms are usually headache, vomiting, palpitations, and confusion.[2] Clinical suspicion is very important in the diagnosis of CO poisoning, but definitive diagnosis is made by measurement of carboxyhemoglobin (COHb) levels.[3]

Both normobaric oxygen (NBO) and hyperbaric oxygen (HBO) therapies are accepted methods of treatment for CO poisoning. Patients with mild poisoning symptoms should undergo NBO treatment. For patients who have coma, altered mental status, seizures, focal neurological deficits, acute myocardial ischemia findings, COHb level > 25% (or for pregnant women COHb level > 15%), HBO therapy should be considered.[1]

CO has a 200 times higher affinity for hemoglobin (Hb) than oxygen. Therefore, it leads to the formation of COHb even at low concentrations. The oxygen dissociation curve is shifted to the left, and as a result, tissue hypoxia develops.[4] In addition, CO also causes the formation of free oxygen radicals, directly by cellular damage and by affecting oxidative metabolism.[5,6] Oxidative stress refers to the formation of more reactive oxygen species (ROS) than that is eliminated by cellular defense mechanisms (antioxidants).[6,7]The increase in reactive oxygen species and free radicals in cells is a major cause of cell damage. Reperfusion after ischemia also increases cellular damage produced by the ischemia due to increased ROS.

There are various opinions on the mechanism of long-term harm of carbon monoxide poisoning. There is no consensus on who should be given hyperbaric oxygen therapy.

The aim of this study is to determine oxidative stress developed in CO poisoning, to measure oxidant and antioxidant parameters, and to study the effects of the NBO and HBO treatments on these parameters.

Materials and Methods

This study was conducted in a Training and Research Hospital. The number of patients admitted to the emergency department annually is approximately 144,000. The study was designed as a prospective observational study. Patients over the age of 18 years who were admitted to our emergency department and diagnosed with CO intoxication during the study period were included in the study. The definitive diagnosis of

CO poisoning was made according to the COHb level in the venous blood gas analysis. Blood gas analysis was made with the analyzer Roche COBAS b221© (Germany) that is available in the emergency department laboratory. COHb levels were measured in patients suspected to be poisoned according to the clinical findings. Patients who had serum COHb levels above 10% in smokers and above >5% in non-smokers were diagnosed with CO poisoning. These patients were informed about the research study. Patients who accepted to participate were included in the study. The patients who are younger than 18 years of age, who didn't accept to participate or who resigned from the study, patients with a history of malignancy, with a diagnosis of an acute inflammatory disease or active infection were excluded from the study. The control group consisted of 50 healthy volunteers that work in our hospital. Informed consent was obtained from all participants.

Firstly demographic data of the patients, date, time, and type of transportation used to come to the emergency department (ambulance or non-ambulance) were recorded in the study form. Then the patient's history (previous diseases, drugs used) and smoking habits were recorded. The source of CO (stove, combi-boiler, water heater, water pipe, exhaust gases, etc.) and exposure time were asked and recorded. The patients' complaints on admission were also recorded (seizures, headache, dizziness, nausea, vomiting, syncope, changes of consciousness, and chest pain). The patients' vital signs, physical examination and detailed neurological examination findings, laboratory results, the type of treatment (NBO or HBO), total duration of treatment, and consultations were recorded in the study forms. The clinician responsible for the treatment of the patient decided on the need for HBO therapy. For patients who have coma, altered mental status, seizures, focal neurological deficits, acute myocardial ischemia findings, COHb level > 25% (or for pregnant women COHb level > 15%), HBO therapy was chosen. All patients who have been treated with HBO have also received NBO during the time they spent in ER.

Routine laboratory tests and peripheral venous blood samples of 5 mL were collected on admission to the emergency department and at the end of the 24th hour after the oxygen therapy. The samples were kept at room temperature for 10-15 minutes in the emergency laboratory and then centrifuged at 3000 rpm for 10 minutes. The obtained sera were placed into a second tube and stored at -80 ° C freezer until the time of analysis.

The oxidative stress parameters total oxidant status (TOS), total antioxidant status (TAS), paraoxonase (PON), serum paraoxonase (SPON), arylesterase (ARES), and thiol (TTL) levels were analyzed.

Measurement of the total oxidant status (TOS)

The TOS of plasma was measured using a novel automated colorimetric method described by Erel (2005). The results are expressed in terms of micromolar hydrogen peroxide equivalent per liter (μmol H_2O_2 Eqv./L).[8]

Measurement of the total antioxidant status (TAS)

Serum TAS was measured using a novel automated colorimetric measurement method developed by Erel. The results are expressed as millimolar Trolox equivalent per liter.[9]

Measurement of PON-SPON and Arylesterase

Paraoxonase and arylesterase activities were measured using commercially available kits (RelassayR, Gaziantep, Turkey).[10] Paraoxonase activity was expressed as U/L serum. Phenylacetate was used as a substrate to measure arylesterase activity. One unit of arylesterase activity was defined as 1 µmol phenol generated / min under the above conditions and expressed as KU/L serum.[11]

Thiol analysis

Serum total thiol concentration or sulfhydryl groups (SH) were measured by the methods originally described by Ellman (1979) and modified by Hu (1994). The result was expressed in µmol/L.[12,13]

Statistical Analysis

The normal distribution of continuous variables in the study was assessed by the Shapiro-Wilks test. The descriptive statistics for continuous variables with normal distribution are expressed by mean± standard deviation, and the descriptive statistics of the variables not normally distributed or discrete are expressed by the median, interquartile range (IQR), and minimum-maximum values. The categorical variables obtained in the study were expressed as numbers (n) and percentages (%). In the comparisons of the continuous and discrete quantitative data of two independent groups Mann-Whitney U test or independent samples, t-test was used. In the comparison of 3 or more independent groups, Kruskal-Wallis test or Analysis of Variance (ANOVA) was used. In the comparison of continuous and discrete quantitative data in dependent groups, paired Wilcoxon Signed Rank test and two paired-samples t-tests were used. IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and MS-Excel 2007 were used for statistical analysis and calculations. A value of $p< 0.05$ was considered statistically significant.

Results

Approximately 72,000 patients were admitted to the emergency department of Training and Research Hospital during the study period. 1270 (1,76%) of these patients were admitted because of poisoning and, 108 (0.15%) of them were diagnosed with CO poisoning. CO poisoning (n = 108) constituted 8.50% of all poisoning cases (n = 1270). The study group consisted of 71 patients who agreed to participate in the study, and the control group consisted of 50 healthy volunteers among our hospital employees, and a total of 121 people were included in the study. The remaining 37 of 108 patients diagnosed with CO poisoning were excluded from the study because 17 of them did not accept to participate, 5 of them had malignancy or active infection, 10 of them were under the age of 18, and 5 of them resigned during the study.

The study group included 71 patients (58.67%), and the control group included 50 healthy individuals (41.32%). The gender distribution of the individuals was similar in the groups (p=0.656). The mean age of individuals in the patient group was 41.3±12.9 years (range 18-65), and the mean age of the individuals in the control group was 30.5±10 years (range 18-53). The average age of individuals in the patient group was older than the control group (p <0.001). There was no significant difference between the study and control groups in terms of conditions that may affect the oxidative stress parameters such as coronary artery disease, hypercholesterolemia, hypertension, neurological disorders, diabetes, liver and kidney disease, peripheral vascular disease, lung disease, multiple sclerosis, iron deficiency anemia, and smoking status.

The mode of transportation was an ambulance for 24 (33,80%) of the patients. Time of admission was between 8-16 in 15 (21,12%) patients, 16-24 in 13 (18,30%) patients, and 24- 8 in 43 (60.56%) patients. The Source of CO exposure was combi boiler in 56 (78,87%) patients, whereas stove was responsible in 14 (19.71%) patients. In 1 (1.40%) patient, the source was unidentified. HBO treatment was used in 11 (15.49%) patients.

The mean duration of exposure to CO was 5.0 hours (IQR= 2.0; min= 1.0; max= 12.0). One of the patients was pregnant (1.40%). Sixty-two patients had a headache (87.32%), 40 patients had nausea (56.33%), 35 patients had dizziness (49.29%), 21 patients had vomiting (29.57%), 16 patients had a syncope (22.53%), eight patients had altered mental status (11.26%), eight patients had chest pain (11.26%), and one patient had a seizure (1.40%) at the time of admission. The mean COHb levels of those patients presenting with syncope were found to be 28.54± 8.5, and those presenting with a symptom other than syncope were found to be 21.7± 5.8; the difference is statistically significant (p = 0.001). For symptoms other than syncope, there was no statistically significant difference in mean COHb levels between patients who have the particular symptom and patients who don't have the symptom.

Physical examination was normal in 69 patients (97.18%), trauma signs were present in one patient (1.40%), and agitation was observed on neurological examination in one patient (1.40%). Venous blood gas analysis results of the patient group were as follows: Median (IQR) value of Ph in the patient group was 7.38 (0.7) (Min-Max 7.2-7.6). The Median (IQR) value of HCO3 was 22.3 (3.7) (Min-Max 9.2- 29.5). Median (IQR) value of COHB was 23.2 (7,1) (Min-Max 10.0- 50.0). Median lactate level (IQR) was 3 (2,3) (Min- Max 0.4-14).

The most frequently consulted departments were cardiology for 18 patients (25.35%), neurology for five patients (7.02%), and gynecology for one patient (1.40%), respectively. There were no significant differences between those who received hyperbaric therapy and those who did not, in terms of initial lactate levels ($p = 0.135$). A comparison between oxidative stress parameters and antioxidant parameters of the patient and control groups when they were first presented to the emergency department is shown in Table 1.

There were no significant differences between the patients with or without a history of DM, hypertension, CAD, and smokers and non-smokers in terms of TOS, TAS, PON, SPON, ARES, and TTL variable values of the patients on admission.

Blood samples were collected from 33 of the 71 patients, for repeated tests, after 24 hours, and oxidative stress and antioxidant capacity parameters were measured. These 24^{th}-hour measurements could not be obtained for 38 patients, either because follow-up in the emergency department lasted shorter than 24 hours or patients did not accept follow-up for 24^{th} hours. The patients' basal and 24-hour values are presented in table 2.

There was no statistically significant difference between admission and 24^{th}-hour values of TOS, PON, SPON, ARES, and TTL obtained from 33 patients (receiving HBO treatment or not) (Table 2). Mean values of TAS were found to be significantly lower at the 24^{th} hour when compared to admission ($p = 0.044$).

There was no difference between the admission oxidative stress parameters of the patients who have received HBO and NBO. Furthermore, we did not found any significant differences when we compared the 24^{th}-hour oxidative stress parameters of those who received NBO and those who received HBO (Table 3).

COHb values of the patients who were consulted with cardiology were found to be significantly higher ($p < 0.001$). Similarly, mean troponin and CK-MB values of the patients who were consulted with cardiology were found to be significantly higher ($p < 0.001$ and $p = 0.010$, respectively).

Table 1. Oxidative stress and antioxidant parameters of the patient and control groups

	Patient		Control		
	Min; max	**Mean±SD**	**Min; max**	**Mean±SD**	**p**
TOS	0-7.8	2.18-1.73	0-0.89	2.81-2.38	0.177
TAS	1.5-3	2.29-0.30	1.8-3.6	2.46-0.33	**0.006**
PON	50.3-471.2	171.9-95.2	43.9-506.1	193.3-106.6	0.238
SPON	101.9-1423.5	467-297.5	92.5-1457.3	539-340.1	0.213
ARES	40.7-286.7	151.8-53.9	60-382.4	195.8-62.7	**<0.001**
TTL	103.8-343.3	191.1-44	155.8-273.5	209.1-23.3	**0.01**

Table 2. The comparison of basal and 24-hour values (n = 33)

	Time of Measurement				p
	Admission 0. hour		24. hour		
	Min; max	**Mean±SD**	**Min; max**	**Mean±SD**	
TOS	0.0; 8.9	2.4 ± (2.1)	0.1; 7.6	1.44± (1.8)	0.160
TAS	1.5; 3.6	2.3± (0.32)	1.1; 2.7	2.1± (0.38)	**0.044**
PON	43.9; 506.1	180.7± (100.2)	49.1; 513.4	175.1 ±103.8)	0.329
SPON	92.5; 1457.3	496.8 ± (316.4)	106.2; 1427.6	486 (322)	0.142
ARES	40.7; 382.4	170±61.4	18.6; 267.0	158.8±63.4	0.949
TTL	103.8; 343.3	198.2±37.8	38.6; 263.0	177.3±43.3	0.098

Table 3. Comparison of oxidative stress parameters after 24 hours who receive NBO or HBO

	NBO n=27 Mean±SD	**HBO n=6 Mean±SD**	**p**
TOS	1.1± 1.4	2.6±2.9	0.072
TAS	2.2± 0.41	2.2±0.22	0.869
PON	173.1±109.3	186.4±81.3	0.782
SPON	475.8±336	531.8±271	0.706
ARES	155.3±66.3	183.2±17.8	0.334
TTL	179.4±40.6	183.8±17.8	0.799

Discussion

Although CO poisoning has been reported at different frequencies depending on different socio-economic and climatic conditions, it is the most important cause of admissions due to poisoning to emergency departments, especially in the winter. Avşaroğulları et al. reported that approximately 1.2 % of all admissions to emergency departments are cases of poisoning, and CO poisonings consist of 9.5% of these cases.[14] In another study conducted in Turkey, 49 of 623 patients who were admitted to the emergency department because of poisoning (7.9%) were diagnosed with carbon monoxide poisoning.[15] In our study, CO poisonings constituted 8.5% of all poisoning cases; this finding is consistent with the literature.

The ratio of women was 54% in patients with CO poisoning in the study of Sahin et al. and 64% in the study of Keles et al.[16,17] In our study the ratio of women was 60.7%.

In our study, there was no statistically significant difference between the patient and control groups in terms of diseases that may affect the oxidative stress parameters. The mean age of the control group was lower than the patient group because the control group consisted of volunteers working in the hospital.

Non-specific symptoms of CO intoxication include headache, nausea, vomiting, palpitations, dizziness, and confusion. Oxygen-dependent organs (brain and heart) are affected earlier than the other organs.[19] In our study, the most common complaints of the patients, were headache (87.32%), nausea (56.33%), dizziness (49.29%), and vomiting (29.57%), respectively. In another study conducted with 483 patients who were admitted to the emergency department with headaches, non-invasive measurement of COHb was found to be >10% in 6.4% of the patients.[18] The similarity of the symptoms with many other diseases often leads to a missed diagnosis. Therefore, the patients presenting with these symptoms should be suspected in terms of CO poisoning, especially in the months when CO poisoning cases are seen in emergency departments most frequently. Our study was conducted between September and March. During this period, COHb levels were measured in patients who were admitted to the emergency department with symptoms such as headache, dizziness, nausea, vomiting, and syncope to avoid missed diagnoses.

CO poisoning can be diagnosed with a history of exposure, but measuring the COHb level supports the diagnosis. COHb levels may not always be compatible with the severity of poisoning. Some publications suggest that there is a strong correlation between blood COHb levels and the severity of poisoning, whereas others suggest that this correlation is available just in mild poisoning cases.[20-22] In our study, the mean COHb levels are found to be significantly higher in only the patients presenting with syncope when compared to patients who do not present with syncope.

In a study conducted with 80 patients, it is reported that increased lactate levels reflect the severity of CO poisoning in the early period.[23] In our study, the initial median lactate level was found to be 3 in the emergency department. There were no significant differences between those who received hyperbaric therapy and those who did not, in terms of lactate levels (p= 0.135).

The deleterious effects of CO poisoning occur by several different mechanisms: binding of CO to hemoglobin and development of functional anemia, direct cellular toxicity, heme-containing proteins binding, the increase of the oxidants[2,] and late changes that are similar to reperfusion injury.[24]

There is a balance between the oxidant and antioxidant defense systems in the body. Oxidative stress is defined as increased levels of oxidants or a reduction of antioxidant capacity and consequent exposure of the cells to oxidative damage. The organism isn't affected as long as there is a balance between the formation and removal rate of free radicals.[25,26] Oxidative stress plays a role in CO poisoning as well as in the pathophysiology of many other diseases.[26] Oxidative stress plays an important role in both the progression of tissue damage induced by CO and during the ischemic-reperfusion phase.[27,28]

There are only a few studies showing the relationship between CO poisoning and sub-parameters of antioxidants. In our study, TOS was measured as an oxidative stress parameter, and TAS, PON, SPON, ARYL, and TTL levels were measured as indicators of antioxidant capacity. We compared pre and post-treatment levels of oxidative stress parameters of patient and control groups. For this purpose, we also studied the sub-parameters of antioxidants.

Kavaklı et al., in their study conducted with 88 patients with CO poisoning, evaluated total oxidant status (TOS), total antioxidant status (TAS), and oxidative stress index (OSI) of patients at the time of admission. TOS and OSI levels of the patient group were found to be significantly higher than the control group. They stated that oxidative stress parameters might be important as early biomarkers of CO poisoning. There were no significant differences between patient and control groups in terms of TAS levels.[29] In the study of Zengin et al. PON, ARES and -SH levels were found significantly lower in the patient group.[2]

In our study, TAS, TTL, and ARES levels were found to be significantly lower in the patient group when compared to the control group ($p = 0.006$, $p = 0.01$, and $p < 0.001$, respectively). Our findings are consistent with the study of Zengin et al. Average SPON and PON levels were also lower in the patient group, but the difference was not statistically significant. We believe that the low levels of antioxidants in patients are due to consumption. The results of our study support that oxidative balance turns against antioxidants in cases of CO poisoning.

In our study, there were no statistically significant differences between patient and control groups in terms of the TOS levels. We attribute the TOS levels of the patients not being as high as expected to CO poisonings being diagnosed earlier.

In the study of Kavaklı et al., the TOS and OSI levels significantly decreased 6 hours after treatment, but no change was observed in TAS levels. In the study of Zengin at al. PON, ARYL, and -SH levels of patients increased in 90th and 180th minutes.[30] In our study, the average TOS, PON, SPON, ARES, and TTL levels of the patient group were lower at the 24th hour when compared to initial values, but the difference was not statistically significant. In the patient group, TAS levels were found to be statistically significantly decreased at the 24th hour when compared to the basal values ($p = 0.044$).

The decrease in the TOS levels suggests that the effect of oxidative stress due to CO intoxication ameliorates at the 24th hour after treatment. On the other hand, the continuing decrease of TAS, PON, SPON, ARES, and TTL maybe because the antioxidant capacity has not yet been replaced or reperfusion ischemia is caused by treatment. In our study, we weren't able to measure the 24th-hour values of many patients. The reason for the lack of expected increase in antioxidant levels may also be a result of the patients' profile because the patients who agreed to stay for 24 hours might be the ones who are clinically worse (better patients might have left the study earlier)

The principal method of treatment in CO poisoning is NBO. The indications of HBO therapy are controversial. Several publications suggest HBO therapy for preventing delayed neurological sequelae. However, further studies are needed to support HBO.[30] In our study, 11 patients received HPO treatment. There were no differences in both initial and 24th-hour levels of oxidative stress parameters between the patients who received hyperbaric therapy and normobaric therapy. According to the results of our study, it is not possible to suggest superiority HBO or NBO in terms of oxidative stress in the treatment of CO poisoning.

The aim of oxygen therapy in CO poisoning is to stop the tissue hypoxia despite COHb elevation by increasing O2 saturation in the blood as rapidly as possible. However, it should be noted that hyperoxygenation might also cause a similar situation to reperfusion injury by facilitating the production of ROS. Given that antioxidant levels decrease due to CO poisoning, antioxidant replacement therapy may be effective in addition to oxygen therapy. Several other studies suggest consideration of various antioxidant therapies (e.g., vitamin C, hydrogen gas) in addition to oxygen therapy to prevent reperfusion injury as well as the initial damage.[24] In the study of Zengin et al., it was observed that antioxidant capacity is improved in the course of treatment.[2]

There is not an exact correlation between the COHb levels and the clinical status of the patients. Oxidative stress parameters, together with COHb levels, can be used as early biochemical markers in the assessment of severity and prognosis of poisoning. However, further studies are needed to support this idea.

Limitations of the study

The small number of our sample group is a limitation of our study. The small number of patients who received hyperbaric therapy is another limitation.

Ethical considerations

Ankara Atatürk Training and Research Hospital's institutional ethical review board approved the study protocol on 25/7/2012 (approval number B.30.2.YBÜ.0006.06.01/20).

Conflict of interest statement

The authors declare that there is no conflict of interest. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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