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Original Article *Özgün Araştırma*

EVALUATION OF SYSTEMIC INFLAMMATORY PARAMETERS IN CARBON MONOXIDE POISONING

Karbonmonoksit Zehirlenmelerinde Sistemik İnflamatuvar Parametrelerin Değerlendirilmesi

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ABSTRACT

Objective: The objective of this study is to examine systemic inflammatory blood parameters measured in complete blood count of patients with carbon monoxide (CO) poisoning and to evaluate the relation between the parameters and the severity of poisoning.

Material and Methods: Our study is a retrospective case control study. Data was obtained through hospital automation system. Patients who were detected to have 10% and above carboxyhemoglobin levels were included in the study. Patients' complete blood count parameters, red cell distribution width (RDW), neutrophil/lymphocyte ratios (NLR), platelet/lymphocyte ratios (PLR) and treatments were recorded.

Results: When the control group was compared to patient group, WBC, leukocyte, neutrophil, platelet, NLR and PLR values were higher in the patient group and these differences were statistically significant ($p < 0.05$). Patients were split into two groups in accordance with the severity of their poisoning. No significant differences were observed in terms of laboratory results ($p > 0.05$).

Conclusion: In patients with CO poisoning, values of NLO, PLO and RDW indicate inflammation. We consider that these values do not assume a role in determination of poisoning severity and in shaping of the treatment to be administered.

ÖZ

Amaç: Bu çalışmada karbonmonoksit (CO) zehirlenmesi olan hastalarda tam kan sayımında bakılan sistemik inflamatuvar kan parametrelerinin irdelenmesi ve bu parametreler ile zehirlenme ciddiyeti arasındaki ilişkinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Çalışmamız retrospektif vaka kontrol çalışmasıdır. Veriler hastane otomasyon sisteminden elde edildi. Karboksihemoglobin düzeyi %10 ve üzerinde saptanan hastalar çalışmaya dahil edildi. Hastaların tam kan sayımı parametreleri, kırmızı küre dağılım genişliği (RDW), nötrofil/lenfosit oranı (NLO), platelet/lenfosit oranı (PLO) ve tedavileri kaydedildi.

Bulgular: Hasta grubunda kontrol grubu ile karşılaştırıldığında WBC, lökosit, nötrofil, trombosit, NLO ve PLO değerleri daha yüksekti ve bu farklar, istatistiksel olarak anlamlıydı ($p < 0.05$). Hastalar zehirlenme ciddiyetlerine göre iki gruba ayrıldı, gruplar arasında laboratuar sonuçları açısından anlamlı fark saptanmadı ($p > 0.05$)

Sonuç: NLO, PLO, RDW; CO zehirlenmesi olan hastalarda, inflamasyonu göstermekte olup, zehirlenme ciddiyetini belirlemede ve tedaviyi şekillendirme de rolü olmadığını düşünmekteyiz.

***Keywords**: Carbon monoxide, poisoning, inflammation, emergency service*

***Anahtar Kelimeler**: Karbonmonoksit, zehirlenme, inflamasyon, acil servis*

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KÜ Tıp Fak Derg 2019;21(1):1-8
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INTRODUCTION

Carbon monoxide (CO) poisoning is a critical medical emergency that comprises a significant part of all intoxication cases both in our country and in the world (1). Although carboxyhemoglobin (COHb) which occurs as a result of the direct bonding of CO molecule to hemoglobin and the tissue hypoxia it induces are suggested to be the foremost mechanisms of CO poisoning, its pathophysiology has not been entirely unraveled. Recently, increase of oxidative stress and inflammatory biochemical cascades that comprise the formation of endogenous free oxygen radicals and the existence of conversely formed antioxidant and anti-inflammatory processes have been reported in the literature (2-4). White blood cell count (WBC) is referred as a well-defined inflammatory marker and/or a stress marker. Neutrophil/lymphocyte ratio (NLR), on the other hand, is suggested as a new marker of the inflammatory response (5). A strong association between NLR and acute coronary syndrome, non-ST myocardial infarction, ischemic and hemorrhagic strokes, pulmonary embolism and several types of cancer was detected in terms of mortality (5-8). It was suggested that the ratio of platelet/lymphocyte (PLR) may be utilized as a potential marker for diagnosing thrombotic activity and inflammation in various oncological and cardiac diseases (8-11). Red cell distribution width (RDW) is a measurement of heterogeneities of circulating erythrocytes. High RDW is usually outcome of increased erythrocyte degradation, nutritional deficiency (iron, vitamin B12 and folic acid deficiency), blood transfusion, chronic inflammation and ineffective erythropoiesis contingent upon neurohumoral activation (12-14). Inflammation and oxidative stress alter erythrocyte homeostasis which results in high RDW. Recently, studies concerning the association of RDW with many other diseases such as coronary artery diseases, pulmonary hypertension, chronic obstructive pulmonary disease (COPD), malignancies, epistaxis and sepsis have been carried out. These studies reported that RDW is a marker of mortality and high RDW indicates a poor prognosis (12-14).

Diagnosis of CO poisoning is established through the measuring of COHb level in serum. However, since the measurement of COHb level is an insufficient predictor in terms of envisioning of parameters such as hospitalization and patient outcome, carrying out studies involving different biomarkers and blood parameters that can indicate the severity of CO exposure became mandatory. There are articles in the literature pertaining to predictive values of parameters such as troponin, lactate and copeptin in CO poisoning (15-17).

Our aim in this study is to examine systemic inflammatory blood parameters measured in complete blood count of patients with carbon monoxide (CO) poisoning and to evaluate the relation between the parameters and severity of poisoning.

MATERIALS AND METHODS

Study Population

Our study is retrospective case control study for which we have received the approval of local ethics committee (Date: 23/05/2018, number: 2012-KAEK-15/1675) prior to commencing. All patients above 18 years of age who applied to the Emergency Medical Clinic of Training and Research Hospital between the dates of September 01–January 31 2018 and diagnosed with CO poisoning were included in the study. Study group was constituted by means of retrospective scanning of hospital automation system (Akgün Health Information System®) and out of patients whose venous blood gas samples showed 10% and above COHb levels and whose ICD diagnosis was established as carbon monoxide poisoning. Demographical data, patients' complaints, systemic and neurological examination findings, complete blood count parameters (Hemoglobin, neutrophil, lymphocyte, platelet, red cell

distribution width (RDW), NLR, PLR, administered treatment type [depending on requirements normobaric (NBOT) or hyperbaric oxygen therapy (HBOT)] belonging to patients were acquired through hospital automation system and patient files. Acquired data was recorded in the study form.

Patients were split into 2 groups according to the severity of poisoning;

a) Mild Poisoning: Patients with symptoms that last 4-6 hours and can heal spontaneously (Headache, nausea, vomiting, fatigue, lack of concentration, visual impairment), patients treated only with NBOT,

b) Moderate-Severe Poisoning: Patients with prolonged symptoms (Chest pain, shortness of breath, confusion, syncope, prostration, tachycardia, tachypnea), patients with life-threatening symptoms (Hypotension, dysrhythmia, myocardial ischemia, non-cardiogenic pulmonary edema, seizures, coma, cardiac arrest, respiratory arrest) and patients who require HBOT and/or treated with HBOT were accepted as moderate-severe poisoning.

Study Exclusion Criteria:

Patients with incomplete data

Patients with oncologic or hematologic disease

Patients with chronic inflammatory diseases (Rheumatoid arthritis, vasculitis, etc.)

Pregnant patients

Patients with recent myocardial infarction (<30 days),

Patients with severe renal disease (GFR <30), severe liver disease

Immunosuppressed patients,

Patients with history of malignancy

The control group consisted of persons who admitted to our emergency department during the same period with a COHb level of less than 5% and who had no disease.

Laboratory Parameters

Our emergency services utilize heparin containing injectors in drawing venous blood gas from patients with the suspicion of carbon monoxide poisoning and samples are processed by using Gestat 1825 (Japan) device, while complete blood count is carried out with Abbott CellDyn 3700 (USA) device. RDW was analyzed using an automated blood cell counter. The NLR was calculated as the ratio of neutrophil count to lymphocyte count, whereas, the PLR was calculated as the ratio of platelet count to lymphocyte count.

Statistical Analysis

Throughout the study analysis of all gathered data was conducted using IBM SPSS16.0 (Chicago, IL, USA) statistics software. Conformance examination of discrete and continuous variable distribution to normal distribution was carried out by means of Kolmogorov Smirnov Test. Since the data did not show conformance to normal distribution, median values and interquartile range were shown as (IQR, 25%-75), whereas, categorical variables were shown as case count and as (%). Categorical variables were subjected to evaluation through Chi-Square Test, whereas, continuous variables were assessed by means of Mann Whitney U Test.

For $p<0.05$ results were considered statistically significant.

RESULTS

Three hundred and eighteen patients admitted during the period of study. One hundred and six patients with incomplete data were excluded from the study. In total, 212 patients and 145 healthy voluntary subjects were included in the study. Male gender constituted 35.4% of the patient group and 37.2% of the control group. Patient and control groups were similar in terms of age and gender. The most common complaint was headache. Demographical data and results of patient and control groups are given in Table 1.

KÜ Tıp Fak Derg 2019;21(1):1-8
Doi: 10.24938/kutfd.429395

When WBC, leukocyte, neutrophil, lymphocyte, platelet, NLR and PLR values of both patient and control groups were compared, all values in the patient group were higher and these differences, apart from lymphocyte values, were statistically significant (Table 2).

Patients were split into two groups in accordance with the severity of their poisoning. No significant differences were observed in terms of laboratory results ($p > 0.05$) (Table 3).

Table 1: The demographic characteristics of the groups

Age, Median	(IQR 25-75)
Patient (n=212)	40 (30-50)
Control (n=145)	37 (30-48.5)
Gender (male), n (%)	
Patient (n=212)	75 (%35.4)
Control (n=145)	54 (%37.2)
COHb level (%), Median (IQR 25-75)	21.05 (15-28.8)
Common presentation symptoms, [n (%)]	
Headache	171 (80.6%)
Nausea/vomiting	139 (65.5%)
Dizziness	81 (38%)
Syncope	27 (12.3%)
GCS score, Median (IQR 25-75)	14.67 (14-15)
Hyperbaric oxygen therapy, [n (%)]	53 (25%)
Troponin, Median (IQR 25-75)	1.8 (0.4-4.1)

COHb: Carboxyhemoglobin GCS: Glasgow coma score

KÜ Tıp Fak Derg 2019;21(1):1-8
Doi: 10.24938/kutfd.429395

Table 2: Laboratory findings of the patients and control subjects

	Patient	**Control**	p value
	Median (IQR 25-75)	Median (IQR 25-75)	
WBC (10^3/µL)	9.3 (7.70- 11.8)	7.8 (6.4-9.6)	<0.01
Neutrophyl (10^3/µL)	5.9 (4.4-8)	4.6 (3.6-6)	<0.01
Lymphocyte (10^3/µL)	2.4(1.7-3)	2.1 (1.8-2.7)	0.12
RDW (%)	15.5 (14.8-16.1)	14.4 (13.4-15.4)	<0.01
Platelet (10^3/µL)	246.5 (214.2-294.7)	233 (198.5-279.5)	<0.05
NLR	2.39 (1.62-3.91)	2 (1.5-2.9)	<0.01
PLR	108.5 (77.1-141.5)	105.2 (83.5-136.6)	0.03

WBC: White blood cell RDW: Red blood cell distribution NLR: Neutrophile lymphocyte ratio, PLR: Platelet lymphocyte ratio

Table 3: Laboratory findings according to severity of toxicity

	Moderate-severe toxicity (n= 53)	**Mild toxicity** (n=159)	**p value**
	Median (IQR 25-75)	Median (IQR 25-75)	
WBC (10^3/µL)	8.9 (7.7- 12.1)	9.3 (7.7-11.8)	0.68
Neutrophile (10^3/µL)	5.530 (4.2-7.4)	6090 (4.6-8)	0.26
lymphocyte (10^3/µL)	2.460 (1.8-3.4)	2350 (1.7-3.02)	0.35
RDW (%)	15.4 (14.5-16.1)	15.6 (14.9-16.2)	0.18
Platelet (10^3/µL)	247 (210.528.2)	246 (214-295)	0.66
NLR	2.10 (1.53-3.39)	2.41 (1.63-3.95)	0.23
PLR	96.5 (71.9-136.4)	108.4 (81.1-142.4)	0.34

WBC: White blood cell RDW: Red blood cell distribution NLR: Neutrophile lymphocyte ratio, PLR: Platelet lymphocyte ratio

DISCUSSION

In this study in which we evaluated systemic inflammatory parameters measured in complete blood count of patients with carbon monoxide poisoning and the relation between these parameters and poisoning severity we consider that we have obtained 2 essential outcomes. Initially, we determined that out of both groups we created (Patient group and control group) NLR, PLR, RDW values in the poisoning group were statistically significantly higher. This particular result we obtained substantiates the very existence of oxidative stress increase and inflammatory condition comprising endogenous free oxygen radicals, antioxidant and anti-inflammatory processes in CO poisoning cases. Secondly, we did not encounter any significant differences in terms of these parameters in HBOT administered moderate/severe poisonings compared to mild CO poisoning. Although the values

KÜ Tıp Fak Derg 2019;21(1):1-8
Doi: 10.24938/kutfd.429395

of NLR, PLR and RDW show an increment in patients with CO poisoning, we think that these parameters do not assume an essential role in determination of poisoning severity and in shaping of the HBOT.

In carbon monoxide poisonings, hypoxic mechanisms histopathologically become a part of the activity and composed metabolic products allow the development of clinical findings and enable physicians to determine the severity of poisoning (3). However, markers haven't reached the sufficient level for the exact determination of exposure severity. Therefore, new markers that are set into motion for the further investigation of inflammation severity are subjected to research. Particularly, measuring of free radicals resultant of tissue hypoxia, ischemia and/or mediators which are released in case of perfusion recently became an intriguing subject; these are considered to assume an assistive role in determination of poisoning level (18). Lately, levels of PLR, NLR and RDW which became crucial markers of inflammation have been examined in a variety of diseases (6,9,13). Recently, NLR has been reported to be in association with physiological stress in the literature. It was suggested that NLR may be utilized as a marker in diagnosis and establishing a prognosis for cases involving infectious tables such as sepsis, pancreatitis, Behcet's disease, atrial fibrillation and cerebrovascular diseases (6-8). PLR which is a marker that demonstrates chronic inflammation was associated with major adverse cardiovascular outcomes and it was further suggested that it may be an independent marker of mortality in some oncologic diseases (9,19). In our study, we detected a significant increase in NLR and PLR values of patients with CO poisoning. We consider that this increment substantiates the existence of physiological stress in CO poisoning. However, we did not observe a relation between these parameters and the severity of poisoning. Depending on the structural complexity of the inflammatory process, not redounding of systemic affection on blood parameters during the acute period may be one of the many possible reasons of this outcome. Resembling to our findings, in a study carried out by Günaydın et al. regarding the CO poisonings, it was reported that no association between severity of poisoning and prognosis was present (20).

PLR and NLR values showed a similar increment and RDW was determined to be associated with inflammatory processes. It was further suggested that increased RDW may be associated with inflammatory markers such as interleukin-6 and tumor necrosis factor (TNF) and these proinflammatory cytokines may suppress the growth of erythrocytes and can shorten half-lives of neutrophils and lymphocytes (21). In the study of Turkdoğan et al. it was reported that CO exposure could constitute a significant increment on RDW levels (22). In our study we detected a significant increase in RDW levels upon CO exposure in a similar way. Based on this result we think that as in other inflammatory parameters, increased RDW represents increased oxidative stress as it is suggested in CO poisoning cases. In Turkdoğan's study, it was suggested that in non-anemic patients, increased RDW may be a predictor in demonstrating poisoning complications, however, no analysis or data was provided regarding this subject (22). In our study credibility of this prognosis was also investigated, however, it was determined that there was no association between increased RDW and the severity of poisoning and complications either.

In our study, we demonstrated the fact that there is a statistically significant difference between these two groups in terms of these parameters, we think that this difference is not clinically significant, only that this elevation reflects the inflammatory process of carbon monoxide poisoning. We also did not detect a relationship between these parameters and severity of poisoning. We think that NLR, PLR and RDW indicate inflammation in patients with CO poisoning and further consider that this assumes no role in determination of poisoning severity and in shaping of the treatment.

Limitations

Our study is single center retrospective study in which the data was obtained through patient files. Our study population was not that large. We could not determine the cigarette smoking status of the patients. We analysed the patients with CO poisoning, carboxyhemoglobin levels above 10% as CO poisoning. Inflammatory process involves a certain complexity and other inflammatory parameters were not subjected to evaluation.

REFERENCES

1. Akca H, Tuygun N, Polat E, Karacan CD. Acute carbon monoxide poisoning: Experience of eight years. Eurasian J Emerg Med. 2015;14:189-91.
2. Emektar E, Ramadan H, Yuzbasioglu Y, Vural S, Coskun F. Use of lactate clearance in determining serum lactate levels and effectiveness of treatment in carbon monoxide poisonings Kırıkkale Üniversitesi Tıp Fakültesi Dergisi. 2017;19(2):60-5.
3. Mannaioni PF, Vannacci A, Masini E. Carbonmonoxide: the bad and the good side of the coin, from neuronal death to anti-inflammatory activity. Inflamm Res. 2006;55(7):261-73.
4. Corbacioglu SK. New potential-treatment options in brain injury due to acute carbon monoxide poisoning in future. J Neurolog Sci. 2016;369:292-3.
5. Soylu K, Gedikli O, Ekşi A, Avcıoğlu Y, Soylu A, Yüksel S et al. Neutrophil-to-lymphocyte ratio for the assessment of hospital mortality in patients with acute pulmonary embolism. Arch Med Sci. 2016;1;12(1):95-100.
6. Lok U, Gulacti U. The predictive effect of the neutrophil-to-lymphocyte ratio (nlr) on the mortality of acute ischemic stroke and its subtypes: a retrospective cross-sectional study. Eurasian J Emerg Med. 2016;15:69-72.
7. Wasilewski J, Pyka L, Hawranek M, Osadnik T, Kurek A, Skrzypek M et al. Prognostic value of neutrophil- to-lymphocyte ratio in predicting long-term mortality in patients with ischemic and nonischemic heart failure. Pol Arch Med Wewn. 2016;126(3):166-73
8. Emektar E, Corbacioglu SK, Dagar S, Uzunosmanoglu H, Safak T, Cevik Y. Prognostic value of the neutrophil-lymphocyte and platelet-lymphocyte ratios in predicting one-year mortality in patients with hip fractures and aged over 60 years. Eurasian J Emerg Med. 2017;16:165-70.
9. Toprak C, Tabakci MM, Simsek Z, Arslantas U, Durmus HI, Ocal L et al. Platelet/lymphocyte ratio was associated with impaired myocardial perfusion and both in-hospital and long-term adverse outcome in patients with ST-segment elevation acute myocardial infarction undergoing primary coronary intervention. Postepy Kardiol Interwencyjnej. 2015;11(4):288-97.
10. Dogan NO, Akinci E, Gumus H, Akilli NB, Aksel G. Predictors of in hospital mortality in geriatric patients presenting to the emergency department with ischemic stroke. Clin Appl Thromb Hemost. 2016;22(3):280-4.
11. Koh CH, Bhoo-Pathy N, Ng KL, Jabir RS, Tan GH, See MH et al. Utility of pre-treatment neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as prognostic factors in breast cancer. Br J Cancer. 2015;113(1):150-8.
12. Karabulut AE, Cevik Y, Emektar E, Corbacioglu SK, Dagar S, Yardim O. Analysis of mean platelet volume and red blood cell distribution width in recurrent epistaxis, Turk J Emerg Med. 2018;18:67-70.
13. Avci E, Kiris T, Demirtas AO, Kadi H. Relationship between high-density lipoprotein cholesterol and the red cell distribution width in

patients with coronary artery disease. Lipids Health Dis. 2018;17(1):53.

14. Kim CH, Park JT, Kim EJ, Han JH, Han JS, Choi JY et al. An increase in red blood cell distribution width from baseline predicts mortality in patients with severe sepsis or septic shock. Crit Care. 2013;17(6):R282.
15. Das M, Cevik Y, Erel O, Corbacioglu SK. Ischemia-modified albumin levels in the prediction of acute critical neurological findings in carbon monoxide poisoning. The Kaohsiung J Med Sci. 2016;32(4):201-6.
16. Irem G, Cevik Y, Keskin AT, Emektar E, Demirci OL, Şafak T et al. Copeptin levels in carbon monoxide poisoning. Turk J Med Sci. 2017;47(2):653-7.
17. Cakir Z, Aslan S, Umudum Z, Acemoglu H, Akoz A, Turkyilmaz S et al. S-100beta and neuron-specific enolase levels in carbon monoxide-related brain injury. Am J Emerg Med. 2010;28(1):61-7.
18. Akyol S, Gulec MA, Erdemli HK, Akyol O. A new therapeutic approach for carbon monoxide poisoning: Antioxidants. Toxicology. 2015;336:34-5.
19. Zhang Y, Lu JJ, Du YP, Feng CX, Wang LQ, Chen MB. Prognostic value of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in gastric cancer. Medicine (Baltimore). 2018;97(12):e0144.
20. Günaydın YK, Vural K, MA Ok, Katırcı Y, Kocaşaban DÜ, Yiğit Y et al. Comparison of carbon monoxide poisonings originated from coal stove and natural gas and the evaluation of Neutrophil/Lymphocyte ratio. Dicle Med J. 2015;42(3):299-304.
21. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med. 2009;133(4):628-32.
22. Turkdogan KA, Eren SH, Sogut O, Karabacak M, Yigit M, Gülen B et al. Red cell distribution width in carbon monoxide poisoning: Relationship with markers of ineffective erythropoiesis, inflammation. Acta Medica Mediterranea. 2014;30(5):1075-9.