RED CELL DISTRIBUTION WIDTH IN CARBON MONOXİDE POISONING: RELATIONSHIP WITH MARKERS OF INEFFECTIVE ERYTHROPOIESIS, INFLAMMATION

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ABSTRACT

Aims*:Carbon monoxide (CO) poisoning is very common. Although it causes death in some cases, the pathophysiologic mechanisms that generate these fatal complications are still not fully understood. No study has directly focused on the indicators of severe complications resulting from CO poisoning; therefore, we investigated red cell distribution width (RDW), which is an indicator of systemic inflammation in patients with CO poisoning.*

Methods*: A total of 429 patients (207 males and 222 females) who experienced CO poisoning between July 2009 and February 2013 were examined.*

Results*: The control group comprised 23 males and 16 females (a total of 39 patients). The RDW level was significantly higher in the CO poisoning group; this increase may indicate the progression of anisocytosis due to CO poisoning. The white blood cell (WBC) level (9.9 ± 3.4 vs 8.5 ± 2.9 x 103/mL, respectively; p = 0.01), hemoglobin (13.7 ± 1.7 vs 12.9 ± 1.1 g/dl, respectively; p < 0.01) and MCHC (34.2 ± 1.1 vs 35.1 ± 1.6, respectively; p < 0.01) were critically higher in the group with CO poisoning.*

Conclusions*: Our data suggest that the hypoxia in patients subjected to CO exposure resulted in significantly elevated red cell distribution width levels. The increasead red cell distribution width levels on admission may indicate the onset of complications due to CO exposure in patients without anemia.*

Key words*: Carbon monoxide poisoning, red cell distribution width.*

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Introduction

Carbon monoxide (CO) is a lethal gas that is made up of one carbon and one oxygen atom linked by a triple bond consisting of two covalent bonds and one dative covalent bond. Carbon monoxide usually fuses evenly in unstable air[(1)]. Carbon monoxide poisoning is common and can cause many health problems, including those involving multiple organ systems (e.g., lung, peripheral, and central nervous system); if undetected, it can result in death[(2)]. Neurologic and cardiovascular problems are common. Unfortunately, most of the symptoms are not always specified and frequently go unnoticed[(3)].

The oxygen-carrying capacity of Hb is affected by CO in two ways. First, CO competitively inhibits O_2 bindings to hemoglobin. It prevents the 02 from being transported to, and supplementing, the tissues. CO leads to a relative anemia, causing asphyxia and tissue hypoxia[(3,4)].

Red cell distribution width (RDW) is a parameter that measures variation in red blood cell size or red blood cell volume. The RDW is usually checked when it is believed that someone may have anemia. An elevated RDW (red blood cells of unequal size) is known as anisocytosis[(5)].

Recent studies have concluded that, in addition to being associated with the diagnosis of anemia, RDW is affiliated with patient diagnoses of cardiac

arrest, pneumonia, critical illness, pulmonary embolism, congestive heart failure, and acute myocardial infarction[6-11]. The means of elevated RDWs in these patients is unknown, but it has been proposed that an increased RDW is related to the inflammatory process. It has been reported that an elevated RDW is associated with inflammatory markers, such as interleukin-6 and tumor necrosis factor, and that pro-inflammatory cytokines could repress the growth of red blood cells and decrease the half-life of red blood cells, which consequently produces an increased RDW[12, 13].

Red cell distribution width (RDW) is a quantitative measure of anisocytosis. Higher RDW values indicate greater variations in size; an elevated RDW (red blood cells of unequal size) is known as anisocytosis[14].

We encountered leukocytosis, erythrocytosis, anemia, pernicious anemia, thrombotic thrombocytopenic, and purpura as laboratory findings in our study of CO poisoning.

We noted that systemic inflammation might be a complication of acute CO poisoning. As far as we know, no study exists that has studied RDW in patients with acute CO poisoning. Therefore, focused on the presumption that RDW is an inflammation marker in patients with CO poisoning.

We contemplated that RDW, as a marker of inflammation, may be associated with anemia and hypoxia in CO poisoning. Thus, a study was conducted to identify the impact of admission red cell distribution width levels in the psychopathology of patients with CO poisoning.

Methods

From June 2009 to March 2013, a total of 490 patients were diagnosed with CO poisoning at the Emergency Department of Bezmialem Vakif University School of Medicine, Cumhuriyet University School of Medicine, and Isparta State Hospital. Yet, only 429 patients were included in the study because of exclusion criteria and laboratory mistakes. Of the 429, 222 were female and 207 were male, with an average age of 34 ± 22 years. An age, gender-matched control group comprised 39 patients (23 male, 16 female with an average age of 39 ± 12 years). All patients agreed to this study and gave their full consent; in addition, the study was approved by the institutional ethics committee.

Some reasons for excluding patients from the study include a history of acute or chronic renal and liver disease, heart failure, valvular heart disease, atherosclerotic heart diseases, peripheral arterial disease, obesity, diabetes mellitus, history of malignancy, chronic hematological diseases, acute or chronic inflammatory disease, autoimmune disease, and drug use affecting RDW. Furthermore, patients who were admitted to emergency care in need of urgent hyperbaric oxygen treatment and pronounced dead in the emergency room were not included in the study.

Cases were chosen from the Bezmialem Vakif University School of Medicine, Cumhuriyet University School of Medicine and the Isparta State Hospital database. All patients who were admitted with a diagnosis of CO poisoning were included. Information about, and medical history of, patients, such as age and gender, were obtained from medical records. Samples of blood were taken to find biochemical markers, and blood cell analyses were performed. The blood of patients admitted to the emergency room with likely CO poisoning were usually studied within 15 minutes. RDW and other blood samples for platelet indices measurement were collected in dipotassium ethylene diamine tetra acetic acid (EDTA) tubes and analyzed with the same type automatic blood counter (Beckman Coulter).

Statistical analysis

Data were analyzed with the SPSS software version 15.0 for Windows. Continuous variables from the study groups were reported as mean ± SD. To compare continuous variables, the Student t-test or Mann - Whitney U test were used wherein appropriate. Categorical variables were compared with the x2test. Univariate linear regression model was used to adjust differences in RDW for age and sex in hypertensive crises and controls. Thereafter, linear regression analyses were performed to identify possible association of RDW as a dependent variable with potential confounding factors among two groups with stepwise method. Beta value and its 95% CI were calculated. These confounders were K, ALT, hb, ALP, LDH, WBC, MCHC. A p value less than 0.05 was considered as statistically significant.

Results

The study group consisted of 429 patients with CO poisoning from stove (207 male, 222 female; mean age 34 ± 22 years). There are 39 patients (23

male, 16 female with a mean age 39±12 years) in control group.

There was no statistically significant differences between two groups with respect to age (p= 0.18) and gender (p= 0.24) (Table I). Aspartate transaminase, potassium and calcium levels were comparable between CO poisoning group and control group (Table 1). Alanine transaminase level was higher in control group (22 ± 16 vs 28 ± 25, respectively; p=0.03). Alkaline phosphatase (94 ± 58 vs 42 ± 8 U/L, respectively; p<0.01) and lactate dehydrogenase (163 ± 76 vs 76 ± 15 U/L, respectively; p<0.01) were significantly higher in CO poisoning group compared with control group (Table 1). Similarly, hemoglobin level (13.7 ± 1.7 vs 12.9 ± 1.1 g/dl, respectively; p<0.01) and platelet counts (272 ± 81vs 246 ± 65 x109, respectively; p=0.06) were higher in CO poisoning group (Table 2).

	CO poisoning group	Control group	P
	(n= 429)	(n=39)	
Mean age (year)	34±22	39±12	0.18
Male / Female	207/222	23/16	0.24
Creatinine, mg/dl	0.91±0.22	0.99±0.31	0.05
Sodium (mg/L)	137±3	138±3	0.12
K (mg/L)	4.03±0.50	4.25±0.45	0.01
AST (U/L)	27±25	27±15	0.98
ALT (U/L)	22±16	28±25	0.03
Ca (mg/L)	9.2±0.5	9.4±0.5	0.25
ALP (U/L)	94±58	42±8	<0.01
LDH (U/L)	163±76	76±15	<0.01

Table 1: Demographic and biochemical characteristics of CO poisoning and control groups.
ALP: alkaline phosphatase, ALT: alanine transaminase, AST: aspartate transaminase, Ca: Calcium, K: potassium, LDH: lactate dehydrogenase, Na: Sodium.

The markers associated with inflammations; white blood cell (WBC) level (9,9 ± 3,4 vs 8,5 ± 2,9 x103/mL, respectively; p=0.01) was significantly higher in CO poisoning group than control group. Moreover, RDW was also significantly higher in CO poisoning group (14.1 ± 1.7 vs 12.7 ± 1.8, respectively; p<0.01) (Table 2, figure 1).

K, ALT, Hb, ALP, LDH, WBC, MCHC were different among the groups, and they were entered into linear regression with stepwise method. Among them, MCHC level (Beta= -0.15, 95% CI: 0.43–0.04, p=0.02) and LDH level (beta=0.33, 95% CI: 0.005–0.013, p=<0.001) and hb level (beta=-0.40, 95% CI: -0.56-0.29, p=<0.001) were dependently associated with RDW values.

	CO group	Control group	P
	(n= 429)	(n=39)	
Hemoglobin, g/dL	13.7±1.7	12.9±1.1	<0.01
WBC, x10^3/mL	9.9±3.4	8.5±2.9	0.01
Plt, x103/mm3	272±81	246±65	0.06
MCV, fl	83±6	84±6	0.31
MCHC, g/dl	34.2±1.1	35.1±1.6	<0.01
Rbc, x10^6/mL	4.8±0.5	4.7±0.6	0.4
RDW, %	14.1±1.7	12.7±1.8	<0.01

Table 2: Hematologic parameters in CO poisoning and control groups.
MCV: mean cell volume, MCHC: Mean Corpuscular Hemoglobin Concentration, Rbc: Red blood cell, Plt: platelet, RDW: red cell distribution width, WBC: white blood cells.

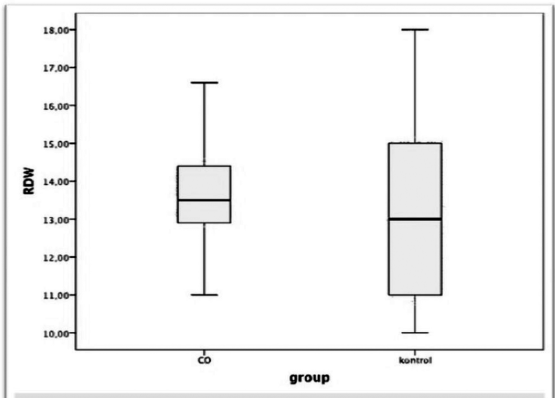

Figure 1: The mean red cell distribution width levels (RDW) in control and CO poisoning groups.

Discussion

In the current study, in patients who had subtle CO poisoning, indicators related to inflammation and anisocytosis were checked. In patients with CO poisoning, we found that WBC, platelet, RBC and RDW were largely higher. On a more significant note, RDW was significantly associated with ALP, MCHC and Hb levels.

Red cell distribution width is a measurable quantity of anisocytosis, a variation on the size of the blood corpuscle. It is included as a part of the complete blood count and is frequently measured by automated hematology analyzers. In conditions in which there is inadequate red cell production, such as hemoglobinopathy, B12 deficiency, folate

deficiency, or iron deficiency, RDW is usually elevated. Other instances in which RDW can be elevated are hemolysis or post-blood transfusion[15].

Several components have been presupposed in the pathophysiological structure of CO poisoning. In regard to the specific mechanism, CO has the capability to bind to the heme group of myoglobin with an affinity 60 times greater than that of oxygen. Therefore, the supply of oxygen to the mitochondria is reduced, which impairs the oxidative phosphorylation and deteriorates the energy source of the myocardium[16]. Through the damage of the mitochondrial respiratory chain at the cytochrome c oxidase level, the mitochondrion isdirectly poisoned[17]. Because of the CO binding to the hemoglobin molecule, alterations in the hemoglobin molecule are made, which inhibits oxygen from being released easily. This causes the tissue to receive less oxygen, resulting in tissue hypoxia[18]. Therefore, neurological and cardiovascular symptoms occur[19]. To the best of our knowledge, a study that has focused directly on inflammation due to CO poisoning is non-existent. This may be because the pathophysiologic components constructing these problems are not wholly understood. One of these components is that CO poisoning activates nitric oxide and other oxygen-free radicals[20]. Endothelial damage can arise because oxygen-free radicals and can effect blood flow[21]. It is theorized that this oxidative injury is intervened largely by leukocytes. Additionally, in leukopenic rats, lipid peroxidation is constrained after CO poisoning. Subsequent to CO exposure, leukocyte sequestration greatly increases brain microvasculature[22]. A major factor of post-ischemic brain injury is the formation of oxygen radicals during reperfusion[23]. Earlier studies have demonstrated that neutrophils play a role in CO-mediated brain injuries in CO poisoning[24]. In our current study, the number of circulating neutrophils was exceedingly higher in the CO poisoning group. In spite of that, the lymphocyte count in both groups was analogous.

A second component, increased thrombotic tendency, has been reported in patients with CO poisoning[25]. Thom et al. demonstrated that acute CO poisoning causes intravascular neutrophil activation due to interactions with platelets[26]. Similarly, we found that platelet and MPV levels were significantly higher in patients with CO poisoning. We anticipate that the results of our study will support the results of previous studies, although we were unable to determine the exact cause of increased RDW in patients with CO poisoning. To determine the pathophysiological and clinical importance of increased RDW in patients with CO poisoning, more studies will need to be conducted.

Conclusions

Our preliminary study showed that hypoxia in patients subjected to CO exposure led to oxidative stress, which resulted in significantly elevated red cell distribution width levels. On the basis of our data, we conclude that admission red cell distribution width levels, as a marker of inflammation may reflect the presence of CO toxicity and provide an early diagnosis in the absence of anemia in patients with CO poisoning. Future controlled clinical trials conducted with larger samples are needed to support and extend these data.

Study Limitations

There some limitations in this study. First, this study was conducted on a retrospective basis and represented only a tree-center experience. Another limitation is that when a blood sample is collected in an EDTA tube, evaluation of the RDW should be done within 30 minutes. In our study, the blood samples of patients with CO poisoning at the emergency room were usually studied within 15 minutes. This could be a factor. Finally, our study population was not that large. Consequently, it may be a variable in the statistical power of the study.

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