

Prognostic Value of Red Cell Distribution Width in Patients with Organophosphate Poisoning

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Abstract

Aim: The aim of this retrospective study was to investigate the prognostic value of red cell distribution width (RDW) and other hematological parameters measured on admission to the emergency department in patients with organophosphate poisoning.

Materials and Methods: All patients aged ≥ 15 years who were admitted to the emergency department from 2008 to 2013 on account of organophosphate poisoning were included in the study. The written and electronic medical charts of the patients were reviewed. Hematological parameters were recorded. Mechanical ventilation requirement was used as the primary endpoint.

Results: A total of 72 patients were included in the study for evaluation. Mechanically ventilated patients had significantly higher leukocyte counts and RDW levels than non-ventilated patients ($p=0.004$ and $p<0.001$, respectively). The area under the receiver-operating characteristic curve of RDW levels for predicting mechanical ventilation requirement was 0.716 (95% CI: 0.581-0.852, $p=0.010$). RDW had a sensitivity of 73%, specificity of 70%, and negative predictive value of 91% with a cut-off value of 14.5% in predicting mechanical ventilation requirement in patients with organophosphate poisoning.

Conclusion: RDW can be a valuable and easy-to-use parameter in estimating prognosis in the follow-up of patients with organophosphate poisoning. (JAEM 2015; 14: 65-9)

Keywords: Organophosphate, poisoning, RDW, leukocytosis, mechanical ventilation

Introduction

Organophosphates are highly toxic compounds for human beings. Organophosphate poisoning by unintentional or suicidal ingestion is associated with high morbidity and mortality, particularly in developing countries (1). In Turkey, the number of patients with suicidal and unintentional organophosphate poisoning increases in spring and summer months during which many farmers spray their agricultural fields with organophosphate compounds (2, 3). Despite all efforts to improve the management of organophosphate-poisoned patients, organophosphate poisoning is still a major public health problem across the world.

Organophosphates inhibit the acetylcholinesterase enzyme irreversibly, and accumulation of acetylcholine results in a cholinergic syndrome. Salivation, lacrimation, diarrhea, emesis, and vomiting are the main signs and symptoms in patients with organophosphate poisoning due to acute muscarinic and nicotinic effects (4). In addition to their cholinergic effects, organophosphates change the balance

between free radical formation and antioxidant defense mechanisms (5). Management of patients with organophosphate poisoning is based on the use of antidotes and general supportive treatments. In particular, adequate respiratory support is highly essential and life-saving in cases of severe poisoning (4).

Red cell distribution width (RDW) is a measure of the variability in the size of erythrocytes; it reflects anisocytosis and can be easily determined from complete blood count (6). In recent studies, it has been shown that higher RDW levels are associated with poor prognosis in various conditions, such as heart failure, acute coronary syndrome, pulmonary embolism, and pancreatitis (7-9). The exact mechanism underlying the increase in RDW levels has not been defined yet; however, it has been reported that there may be deformation of erythrocyte membranes by acute or chronic inflammation (9). Similarly, acute inflammation and increased oxidative stress seen in organophosphate poisoning can lead to a change in the size and structure of erythrocytes in circulation. As a result, it is expected that RDW levels may be increased in organophosphate poisoning and can thus aid in prognosis.

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The aim of this retrospective study was to investigate the prognostic value of RDW and other hematological parameters measured on admission to the emergency department in patients with organophosphate poisoning.

Materials and Methods

The study was conducted in compliance with the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Necmettin Erbakan University Meram Faculty of Medicine.

Study population

This retrospective cohort study was conducted in the emergency departments of one university hospital and one training and research hospital. All patients aged ≥ 15 years who were admitted to both emergency departments from July 2008 to February 2013 on account of organophosphate poisoning were included in the study.

The diagnosis of organophosphate poisoning was based on the history of exposure to or contact with organophosphates, presence of characteristic cholinergic signs and symptoms of organophosphate poisoning, improvement of signs and symptoms with atropine and oximes, and decreased serum cholinesterase activity.

Treatment protocol

Both centers have a unique treatment protocol for the management of patients with organophosphate poisoning. All patients were treated in compliance with this standard protocol that includes following steps. Initial decontamination procedures were performed, including removal of all clothing, washing the whole body with soap and water, gastric lavage, and treatment with activated charcoal. Patients with cholinergic symptoms such as lacrimation, salivation, and diaphoresis and those with decreased serum cholinesterase levels were treated with intravenous atropine and pralidoxime (1 g intravenous loading and then 500 mg/h infusion).

Study protocol

The written and electronic medical charts of the patients were reviewed. Demographic data, route of exposure, Glasgow Coma Scale (GCS) scores, serum cholinesterase levels, complete blood count results [leukocyte, hemoglobin (Hb), platelet, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and RDW] on admission to the emergency department, mechanical ventilation requirement, length of stay in the hospital, and outcomes were recorded using standard data collection forms. The data collection forms were filled out by one investigator from each center and the accuracy of the data was verified by a third independent investigator.

After the data forms were filled, the hematologic parameters were investigated separately. Mechanical ventilation requirement was used as the primary endpoint. The patients were divided into two subgroups: mechanically ventilated and non-ventilated. The differences in the hematological parameters between the groups were compared.

Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences 16.0 (SPSS Inc., Chicago, Illinois, USA) software. Descriptive statistics were computed for all variables. Quantitative vari-

ables were expressed as the median (interquartile range) and categorical variables were expressed as the number of cases (percentage).

All data were analyzed for normality and all parameters were found to be non-normally distributed. Differences between the mechanically ventilated and non-ventilated patient groups were compared using the Mann-Whitney U test for quantitative variables. Variables found to be significant in univariate analysis with a p value of <0.025 were subjected to multivariate logistic regression analysis.

Receiver-operating characteristic (ROC) curves were used to determine the power of the parameters in predicting mechanical ventilation requirement. The optimal cut-off values for each parameter were determined by using Youden's index (sensitivity+specificity-1). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy rate were calculated for those cut-off values.

Results

In this retrospective study, the charts of 101 patients admitted to the emergency departments on account of pesticide poisoning from July 2008 to February 2013 were reviewed. Twenty-nine patients were excluded from the study because of lack of complete blood count results or serum cholinesterase levels and coexisting diseases, including cancer, hematological diseases, and trauma. A total of 72 patients were included in the study for evaluation.

The median age of the patients was 37.0 (25.5-50.8) years and 40 (55.6%) patients were male. The route of exposure was oral ingestion in 56 (77.8%) patients, inhalation in 12 (16.7%) patients, and transdermal in 4 (5.6%) patients. The median serum cholinesterase level of patients was 887.0 (288.3-1955.3) U/L. The median length of stay in the hospital was 6 (3-8) days and the mortality rate was 9.7%.

Of the 72 patients, 15 (20.8%) required mechanical ventilation support during the treatment period. Mechanically ventilated patients had significantly lower GCS scores and serum cholinesterase levels than non-ventilated patients ($p<0.001$ and $p=0.002$, respectively). Mechanically ventilated patients had significantly higher leukocyte and platelet counts than non-ventilated patients ($p=0.004$ and $p=0.047$, respectively). In addition, mechanically ventilated patients had significantly higher RDW levels than non-ventilated patients ($p=0.010$). Comparison of the evaluated parameters between mechanically ventilated and non-ventilated patients is given in Table 1.

Of the patients, 7 (9.7%) died during the intensive care unit follow-up period. Non-survivors had higher median RDW levels than survivors [15.40 (15.10-16.40) and 14.30 (13.30-16.00), respectively, $p=0.047$].

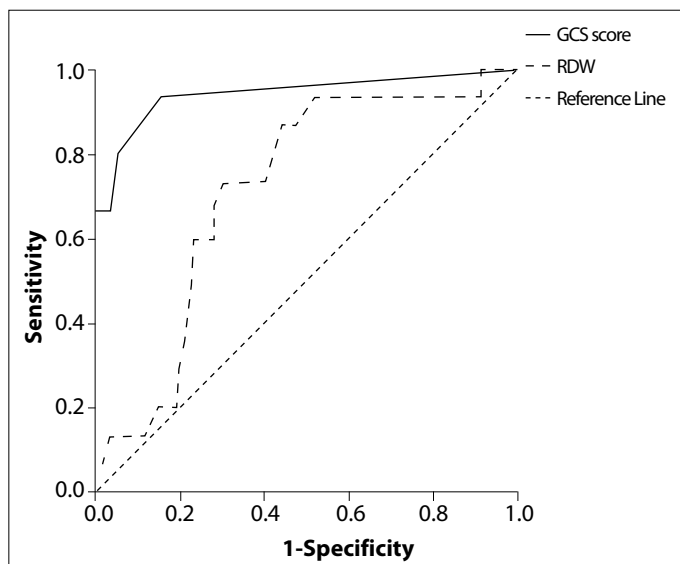
The area under the ROC curve of GCS scores for predicting mechanical ventilation requirement was 0.942 (95% CI: 0.859-1.024, $p<0.001$). The optimal cut-off value was 14. The area under the ROC curve of RDW levels for predicting mechanical ventilation requirement was 0.716 (95% CI: 0.581-0.852, $p=0.010$). The optimal cut-off value was 14.5% (Figure 1). Sensitivity, specificity, NPV, PPV, and accuracy rate of both parameters are given in Table 2.

The area under the ROC curve of leukocyte count for predicting mechanical ventilation requirement was 0.816 (95% CI: 0.699-0.934, $p<0.001$). The optimal cut-off value was 18.70 K/uL. The area under the ROC curve of serum cholinesterase levels for predicting mechanical ventilation requirement was 0.760 (95% CI: 0.638-0.883, $p=0.002$). The optimal cut-off value was 754 U/L (Figure 2). Sensitivity, specificity, NPV, PPV, and accuracy rate of both parameters are given in Table 2.

Table 1. Comparison of the evaluated parameters between the mechanically ventilated and non-ventilated patient groups

Parameters, median (25%-75%)	Mechanically ventilated (n=15)	Non-ventilated (n=57)	p value
Age, years	48.0 (32.5-52.5)	35.0 (24.0-48.0)	0.124
GCS score	10 (5-13)	15 (15-15)	<0.001
Serum cholinesterase, U/L	289.0 (216.0-615.5)	1164.0 (363.0-2211.0)	0.002
Leukocyte, K/uL	19.60 (15.55-24.99)	12.74 (9.59-16.70)	0.004
Hemoglobin, g/dL	14.00 (11.65-14.65)	14.40 (13.30-15.30)	0.192
Platelet, K/uL	283.0 (217.0-345.5)	215.0 (193.0-282.0)	0.047
MCV, fL	83.35 (81.85-88.85)	86.55 (83.90-89.90)	0.398
MCH, pg	27.65 (26.45-29.95)	29.30 (28.05-30.15)	0.145
MCHC, g/dL	32.35 (31.15-33.70)	33.50 (32.40-34.35)	0.086
RDW, %	15.1 (14.3-15.9)	13.6 (12.9-14.9)	0.010
Length of stay in the hospital, days	12.0 (6.5-20.50)	5.0 (3.0-6.0)	<0.001

GCS: Glasgow Coma Scale; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW: red cell distribution width

**Figure 1.** ROC curves of GCS scores and RDW levels for predicting mechanical ventilation requirement

ROC: receiver-operating characteristic; GCS: Glasgow Coma Scale; RDW: red cell distribution width

Glasgow Coma Scale scores, serum cholinesterase levels, leukocyte counts, and RDW levels were factors that predicted mechanical ventilation requirement in univariate analysis. These parameters were further analyzed using multivariate logistic regression analysis. A GCS score of <14, serum cholinesterase levels of <754 U/L, and RDW levels of >14.5% were found to be independent risk factors for predicting mechanical ventilation requirement (Table 3).

Discussion

Although the major mechanism of action in organophosphate poisoning is the inhibition of acetylcholinesterase activity, organophosphate compounds may lead to many clinical effects, including

hepatotoxicity, hemotoxicity, cardiotoxicity, and neurohumoral disturbances (10-13). In experimental and clinical studies, it has been shown that these systemic effects are due to oxidative stress in acute and chronic organophosphate poisoning (5, 14, 15). Oxidative stress is defined as disturbance of the balance between the production of free radicals and the antioxidant capacity of the body (16). It has been reported that more severe poisoning means more production of free radicals and more oxidative stress (5, 10). It has also been shown that increased oxidative stress contributes to an increase in lipid peroxidation and decrease in the phospholipid content of the erythrocyte membrane. As a result, the erythrocyte membrane is damaged and erythrocytes lose their integrity (17). The lifespan of mature erythrocytes is shortened as a result of deformation of their membrane (18). In addition, it has been reported that organophosphate compounds directly inhibit Hb synthesis (10, 19). According to the balance between these pathophysiological mechanisms and the duration and severity of poisoning, different complete blood count results can be obtained.

In our study, there was no statistically significant difference between the patient groups in terms of Hb, MCV, MCH, and MCHC. In some of the experimental and clinical studies, it has been reported that all these parameters remain unchanged in organophosphate poisoning, whereas in other studies, it has been shown that MCH and MCHC values remain unchanged and Hb and MCV values decrease (19-21). The expected blood picture is severe anemia in organophosphate poisoning because of the shortened lifespan of erythrocytes and inhibited Hb synthesis by organophosphates. In our study, we consider that the normal Hb levels of patients with organophosphate poisoning within the first 24 h were possibly due to the non-depleted antioxidant capacity of erythrocytes in the early period of poisoning. In addition, we believe that erythrocytes cannot complete their lifespan, although it is shorter. These results should be confirmed by further prospective and controlled studies.

In our study, we found that mechanically ventilated patients with organophosphate poisoning had higher RDW levels on admission to the emergency department. In experimental studies, different results

Table 2. Parameters for predicting mechanical ventilation requirement

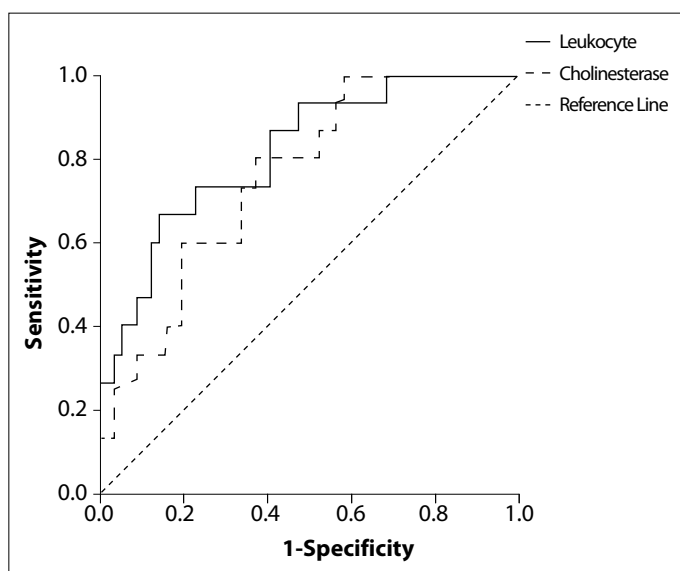
Parameters	Cut-off value	% (95% confidence interval)				
		Sensitivity	Specificity	PPV	NPV	AR
GCS score	<14	80 (57-93)	95 (89-98)	80 (57-93)	95 (89-98)	92 (82-97)
Leukocyte	>18.70 K/uL	67 (42-85)	86 (80-91)	56 (35-71)	91 (84-96)	82 (72-90)
Cholinesterase	<754 U/L	80 (54-95)	63 (56-67)	36 (25-43)	92 (82-98)	67 (56-73)
RDW	>14.5%	73 (48-91)	70 (63-75)	39 (26-49)	91 (82-97)	71 (60-78)

GCS: Glasgow Coma Scale; PPV: positive predictive value; NPV: negative predictive value; AR: accuracy rate; RDW: red cell distribution width

Table 3. Multivariate logistic regression analysis of parameters for predicting mechanical ventilation requirement in patients with organophosphate poisoning

Predictor	β	SE β	χ^2 (Wald)	df	p	Odds ratio
Constant	-7.215	2.141	11.361	1	0.001	
GCS score (<14/ $\geq$ 14)	4.435	1.338	10.982	1	0.001	84.370
RDW (>14.5%/≤14.5%)	3.420	1.474	5.384	1	0.020	30.568
Cholinesterase (<754 U/L/ $\geq$ 754 U/L)	2.864	1.425	4.037	1	0.045	17.525
Leukocyte (>18.7 K/uL/≤18.7 K/uL)	1.583	1.115	2.017	1	0.156	4.871
Test			χ^2	df	p	
Overall model evaluation						
Likelihood ratio test			50.908	4	<0.001	
Goodness-of-fit test						
Hosmer and Lemeshow			4.745	6	0.577	

Cox and Snell $R^2=0.507$, Nagelkerke $R^2=0.791$, overall percentage of correct predictions was 95.8%
GCS: Glasgow Coma Scale; RDW: red cell distribution width

**Figure 2.** ROC curves of leukocyte counts and serum cholinesterase levels for predicting mechanical ventilation requirement

ROC: receiver-operating characteristic

have been reported about RDW levels in organophosphate poisoning (10, 19, 21). A clinical study reported that RDW levels remain unchanged in patients with low-dose organophosphate poisoning (20). In one study in which morphological evaluation of the blood cells

of organophosphate-poisoned rats was performed using scanning electron microscope, it was reported that most of the cells changed to stomatocytes or spherocytes, and increased anisocytosis was a prominent feature (22). In addition, another study showed anisocytosis in rats with organophosphate poisoning (19). Our findings support that anisocytosis occurs in more severe organophosphate poisoning. We found that RDW had a sensitivity of 73%, specificity of 70%, and NPV of 91% with a cut-off value of 14.5% in predicting mechanical ventilation requirement in patients with organophosphate poisoning. We suggest that RDW levels measured on admission to the emergency department can be used as a prognostic marker in patients with organophosphate poisoning.

In our study, we found that patients with more severe poisoning had leukocytosis on admission to the emergency department. Two major mechanisms in acute organophosphate poisoning, cholinergic syndrome and increased oxidative stress, lead to increased leukocyte counts in the body. Experimental and clinical studies have reported that leukocyte counts are increased in organophosphate poisoning (3, 10, 20, 21). In a few clinical studies, it was reported that leukocytosis could be used as a prognostic parameter for predicting the severity of organophosphate poisoning (3, 23, 24). Our findings were in compliance with those reported in the literature; however, we failed to identify leukocytosis as an independent risk factor for predicting mechanical ventilation requirement using multivariate analysis. The clinical value of leukocytosis should be evaluated by further prospective and controlled studies.

Although our primary aim was to investigate the hematological parameters for predicting the severity of organophosphate poisoning, we evaluated the parameters that are routinely used during the follow-up period of patients with organophosphate poisoning, such as GCS scores and serum cholinesterase levels. We found that patients with more severe poisoning had lower GCS scores and serum cholinesterase levels on admission to the emergency department. As a result of multivariate analysis, the GCS score was found to be the most powerful independent prognostic factor for predicting mechanical ventilation requirement. According to our findings, prognosis of patients with organophosphate poisoning whose GCS scores are below 14 on admission to the emergency department appears to be poor.

Study limitations

This was a retrospective study, with relatively few non-survivor cases. We could not analyze the non-survivor group because of the low number of cases. Therefore, the value of RDW in patients with organophosphate poisoning in terms of predicting mortality should be considered in large-scale prospective studies.

Conclusion

In this study, we found that patients with more severe organophosphate poisoning had increased leukocyte counts and RDW levels. These patients also had decreased GCS scores and serum cholinesterase levels. Leukocyte counts and RDW levels measured on admission to the emergency department are considered as valuable and easy-to-use parameters in estimating prognosis in the follow-up of patients with organophosphate poisoning.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Necmettin Erbakan University Meram Faculty of Medicine.

Informed Consent: Due to the retrospective nature of this study, informed consent was waived.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Z.D.D.; Design - Z.D.D., B.C.; Data Collection and/or Processing - M.E., R.Ö., Y.K.G.; Analysis and/or Interpretation - Z.D.D.; Literature Review - Z.D.D., M.E.; Writer - Z.D.D.; Critical Review - B.C.

Conflict of Interest: No conflict of interest was declared by the authors.

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