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TIME-DEPENDENT CHANGES OF HEMATOLOGICAL PARAMETERS IN PATIENTS WITH ACUTE ORGANOPHOSPHATE POISONING

Organofosfat Zehirlenmelerinde Hematolojik Parametrelerin Zamana Karşı Değişimi

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ABSTRACT

Objective: To investigate the prognostic value of the time-dependent changes of hematological parameters in patients with acute organophosphate poisoning.

Methods: All patients admitted to emergency departments from 2010 through 2013 due to organophosphate poisoning were enrolled in the study. Demographic data, route of exposure, serum cholinesterase levels, complete blood count results of 5 consecutive days, mechanical ventilation requirement, length of stay in hospital, and outcomes were recorded.

Results: Mechanically ventilated patients had higher leukocyte and neutrophil counts than non-ventilated patients during the whole follow-up period, and both of them had a trend of decrease in both patient groups. There was no difference between patient groups in terms of lymphocyte counts at day 1, but mechanically ventilated patients had lower lymphocyte counts than non-ventilated patients after day 2. Hemoglobin levels had a trend of decrease during the whole follow-up period in both patient groups.

Conclusion: The parameters obtained from complete blood count can be used as sensitive follow-up parameters in patients with acute organophosphate poisoning by serial measurement.

Key words: Organophosphate, poisoning, leukocytosis, neutrophil-lymphocyte ratio.

ÖZET

Amaç: Bu çalışmada, akut organofosfat zehirlenmesi olan hastalarda hematolojik parametrelerin zamana karşı değişimleri ve parametrelerin prognostik değerinin araştırılması hedeflenmiştir.

Yöntem: Acil servise 2010-2013 yılları arasında organofosfat zehirlenmesi nedeniyle başvuran tüm hastalar çalışmaya dahil edildi. Hastaların demografik bilgiler, zehirlenme yolu, serum kolinesteraz düzeyleri, 5 günlük tam kan sayımı sonuçları, mekanik ventilasyon ihtiyacı, hastanede yatış süresi ve taburculuk durumu ile ilgili bilgileri kaydedildi.

Bulgular: Mekanik ventilasyon ihtiyacı olan hastaların lökosit ve nötrofil sayıları tüm takip süresince ventilasyon ihtiyacı olmayan hastalarda daha yüksekti. Her iki grupta da nötrofil ve lökosit sayılarının zamana karşı değişimi azalma yönündeydi. Gruplar arasında lenfosit sayısı açısından 1. gün anlamlı bir fark tespit edilmedi, fakat 2. günden sonra mekanik ventilasyon yapılan hastalarda lenfosit sayıları daha düşüktü. Her iki grupta, hemoglobin değerleri zamanla azalma eğilimindeydi.

Sonuç: Tam kan sayımından elde edilen parametreler, organofosfat zehirlenmesi olan hastaların takibinde seri ölçümlerle prognostik parametreler olarak kullanılabilir.

Anahtar kelimeler: organofosfat, zehirlenme, lökositoz, nötrofil-lenfosit oranı

INTRODUCTION

Organophosphates are widely used chemicals for killing a variety of pests and are extremely toxic for human beings. In developing countries, intentional and unintentional organophosphate poisonings results in high mortality and morbidity (1,2). Approximately, it counts a total of 200,000 deaths a year due to organophosphate poisoning (3). Organophosphates inhibit acetylcholinesterase in synapses and on erythrocyte membranes, and butyrylcholinesterase in plasma. Acetylcholinesterase inhibition results in accumulation of acetylcholine and overstimulation of acetylcholine receptors in synapses. Due to cholinergic crisis, respiratory failure is suddenly developed and it can be resulted in death, especially in severely poisoned patients The management of patients with organophosphate poisoning is based on the antidote and the general supportive treatments. Especially, the adequate respiratory support given to severely poisoned patients is lifesaving. (3,4).

Although the main mechanism of organophosphate poisoning is the inhibition of cholinesterase,

the systemic effects of organophosphates are due to oxidative stress (5,6). Organophosphates pass through the cell membranes into the cytoplasm and induce the damage to the cellular molecules, including lipids, proteins, and DNA (7). In recent studies, it has been reported that organophosphates can cause anemia and alteration in other hematological parameters (7-11). Although the organophosphate-induced hemotoxicity is a well-known issue, the trend of the alterations in hematological parameters in patients with acute organophosphate poisoning is unstudied.

The aim of this study is to investigate the prognostic value of the time-dependent changes of hematological parameters in patients with acute organophosphate poisoning.

MATERIAL AND METHODS

The study was conducted in compliance with the guidelines of the Declaration of Helsinki and was approved by the local ethical committee.

Patients

This retrospective cohort study was conducted in the emergency departments of one university hospital and one training and research hospital. All patients (15-year-old and older) admitted to both emergency departments from 2010 through 2013 due to organophosphate poisoning and followed up in intensive care units at least five days were enrolled 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

All patients were followed up in an intensive care unit and treated with standard protocols. All clothes of patients were removed and the whole bodies of patients were washed with soap. Gastric lavage and activated charcoal administration were performed to all patients. The patients with cholinergic symptoms like lacrimation, salivation, diaphoresis, and with decreased serum cholinesterase levels were treated with intravenous atropin (dose adjustment made according to presence of atropinization findings) and pralidoxime (1 g intravenous loading and then 500 mg/hour infusion, until muscle weakness and secretions resolved).

Study protocol

The written and electronic medical charts of patients were reviewed. Demographic data, route of exposure, Glasgow Coma Scale scores, serum cholinesterase levels, complete blood count results (leukocyte, neutrophil, lymphocyte, monocyte, eosinophil, basophil, platelet, and hemoglobin values) of 5 consecutive days beginning with admission to emergency department, mechanical ventilation requirement, length of stay in hospital, and outcomes were recorded using standard data collection forms. The data collection forms were filled out by one investigator from both centers 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. Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio were calculated using absolute neutrophil, lymphocyte and platelet counts. Time-dependent changes of hematological parameters in all patients with organophosphate poisoning were evaluated and then the same evaluation was performed between mechanically ventilated and non-ventilated patients.

Statistical analysis

All statistical analysis were performed using SPSS 16.0 (SPSS Inc, Chicago, Illinois, USA) software. Descriptive statistics were computed for all variables. Quantitative variables were expressed as mean ± standard deviation and categorical variables were expressed as number of cases (percentage).

All data were analyzed for normality. The differences between the mechanically ventilated and non-ventilated patient groups were compared using the Student's t-test for normally distributed quantitative variables and the Mann-Whitney U test for non-normally distributed quantitative variables. The changes of variables in time were assessed by the Friedman test and the one-way ANOVA with repeated measures where the test was appropriate.

RESULTS

In this retrospective study, the charts of 75 patients admitted to emergency departments due to organophosphate poisoning from 2010 through 2013 were reviewed. Seventeen patients were excluded from study due to the lack of complete blood count results or serum cholinesterase levels, and four patients were excluded due to concomitant hematological diseases, and trauma. A total of 54 patients were included in the study for evaluation.

The mean age of patients was 38.4±18.6 and 30 (55.6%) of patients were male. The route of exposure was oral ingestion in 41 (75.9%) patients, inhalation in 9 (16.7%) patients, and transdermal in 4 (7.4%) patients. The mean serum cholinesterase level of patients was 1415±1202 U/L. Thirteen (24.1%) of 54 patients required mechanical ventilation support during the treatment period. The mean length of stay in hospital was 7.6±6.4 days and the mortality rate was 9.3%.

When the hematological parameters of all patients were evaluated, it was found that patients with acute organophosphate poisoning

Table 1. The time-dependent changes of hematological parameters in patients with organophosphate poisoning.

	Day 1	Day 2	Day 3	Day 4	Day 5	p value
Leukocyte, K/uL	15.16±7.27	11.39±4.15	9.65±3.86	9.35±3.60	8.75±3.50	<0.001
Neutrophil, K/uL	12.46±7.06	8.93±4.25	7.02±3.73	6.84±3.53	6.13±3.04	<0.001
Lymphocyte, K/uL	1.92±1.40	1.69±0.88	1.81±0.72	1.72±0.73	1.79±0.80	0.074
Monocyte, K/uL	0.97±0.45	0.66±0.43	0.69±0.53	0.65±0.38	0.67±0.50	0.801
Eosinophil, K/uL	0.06±0.06	0.07±0.09	0.09±0.10	0.10±0.10	0.12±0.09	<0.001
Basophil, K/uL	0.04±0.05	0.04±0.03	0.04±0.04	0.04±0.04	0.04±0.04	0.475
Platelet, K/uL	255.5±81.8	224.5±60.7	204.7±53.4	206.9±55.7	211.9±67.0	<0.001
Hemoglobin, g/dL	14.21±1.97	13.19±1.80	12.77±1.76	12.69±1.77	12.71±1.75	<0.001
NLR	10.16±8.31	9.99±14.41	5.33±5.12	5.88±6.53	4.40±3.54	<0.001
PLR	192.2±121.8	209.0±221.9	141.3±97.7	154.5±113.1	139.2±70.9	0.062

NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio

Table 2. The time-dependent changes of hematological parameters in mechanically ventilated and non-ventilated patient groups.

	Day 1	Day 2	Day 3	Day 4	Day 5	p value**
Leukocyte, K/uL						
MV (+)	22.21±9.67	15.53±4.51	12.93±5.30	13.21±4.06	11.67±4.34	0.009
MV (-)	12.92±4.55	10.15±3.15	8.50±2.38	7.91±2.05	7.50±2.16	<0.001
p value *	0.005	<0.001	0.014	<0.001	0.007	
Neutrophil, K/uL						
MV (+)	19.27±9.00	13.48±3.75	12.93±5.30	13.21±4.06	11.67±4.34	0.005
MV (-)	10.29±4.68	7.57±3.38	8.50±2.38	7.91±2.05	7.50±2.16	<0.001
p value*	<0.001	<0.001	0.002	<0.001	<0.001	
Lymphocyte, K/uL						
MV (+)	1.86±1.55	1.14±0.84	1.07±0.46	1.07±0.66	1.36±0.81	0.240
MV (-)	1.94±1.38	1.86±0.84	2.07±0.61	1.96±0.59	1.98±0.73	0.105
p value*	0.511	0.009	<0.001	<0.001	0.023	
Monocyte, K/uL						
MV (+)	0.97±0.65	0.86±0.74	0.93±0.93	0.86±0.61	0.95±0.77	0.465
MV (-)	0.58±0.33	0.59±0.28	0.61±0.25	0.57±0.20	0.56±0.27	0.630
p value*	0.010	0.216	0.245	0.137	0.111	
Eosinophil, K/uL						
MV (+)	0.04±0.06	0.03±0.06	0.01±0.01	0.03±0.06	0.06±0.06	0.074
MV (-)	0.06±0.06	0.08±0.09	0.12±0.10	0.13±0.10	0.15±0.08	<0.001
p value*	0.076	0.028	<0.001	<0.001	0.002	
Basophil, K/uL						
MV (+)	0.06±0.08	0.03±0.02	0.02±0.02	0.03±0.02	0.04±0.04	0.702
MV (-)	0.03±0.03	0.04±0.04	0.04±0.04	0.05±0.04	0.05±0.04	0.544
p value*	0.666	0.320	0.062	0.174	0.347	
Platelet, K/uL						
MV (+)	299±108	237±74	209±62	221±75	219±87	0.007
MV (-)	241±67	221±57	203±51	202±47	209±58	0.001
p value*	0.089	0.430	0.752	0.419	0.883	
Hemoglobin, g/dL						
MV (+)	13.6±2.4	12.6±2.1	11.8±1.8	11.7±2.0	11.5±1.7	0.006
MV (-)	14.4±1.8	13.4±1.7	13.1±1.7	13.1±1.5	13.2±1.5	<0.001
p value*	0.208	0.235	0.030	0.034	0.003	
NLR						
MV (+)	16.11±10.20	18.62±15.45	11.16±5.67	13.58±8.20	8.28±3.90	0.045
MV (-)	8.27±6.72	7.41±13.21	3.28±2.91	2.99±1.93	2.74±1.54	<0.001
p value*	0.007	<0.001	<0.001	<0.001	<0.001	
PLR						
MV (+)	238.5±131.7	320.6±250.3	233.4±135.8	261.9±154.5	191.4±87.7	0.369
MV (-)	177.6±116.4	175.6±204.4	108.9±51.9	114.18±56.1	116.9±48.9	0.030
p value*	0.108	0.007	<0.001	<0.001	0.006	

MV: mechanically ventilated, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio

* p values of the comparison of parameters between mechanically ventilated and non-ventilated patient groups for each day

**p values of the time-dependent changes of the parameters in mechanically ventilated and non-ventilated patient groups

had higher leukocyte, neutrophil, hemoglobin and platelet counts and neutrophil-lymphocyte ratios within the first 24 hours on admission to emergency department. The time-dependent changes of parameters were significant in terms of leukocyte, neutrophil, platelet, and hemoglobin values and neutrophil-lymphocyte ratios (for all, p<0.001). It had seen that all of the parameters had a trend of decrease within 5 days, except eosinophil counts. The time-dependent changes of parameters were tabulated in Table 1.

When the hematological parameters of subgroup patients were evaluated, it was found that mechanically ventilated patients had higher leukocyte and neutrophil counts than non-ventilated patients during the whole follow-up period, and both of them had a trend of decrease in both patient groups (respectively, p=0.009 and p=0.005, in mechanically ventilated patients; for both p<0.001, in non-ventilated patients). There was o difference between patient groups in terms of lymphocyte counts at day 1, but mechanically ventilated patients had lower lymphocyte counts than non-ventilated patients after day 2 (p=0.009, for day 2; p<0.001, for days 3 and 4; p=0.023, for day 5). Although the time-dependent changes in lymphocyte counts was statistically insignificant in mechanically ventilated patients, the minimum lymphocyte counts were measured at days 3 and 4 (p=0.240). The platelet counts had a trend of decrease in both patient groups (p=0.007, for mechanically ventilated patients, and p=0.001, for non-ventilated patients). Hemoglobin levels had a trend of decrease during the whole follow-up period in both patient groups (p=0.006, for mechanically ventilated patients, and p<0.001, for non-ventilated patients). However, the decrease in hemoglobin levels was marked in mechanically ventilated patients, and the differences between groups in terms of hemoglobin levels were statistically significant after day 3 (p=0.030, for day 3; p<0.034, for day 4; p=0.003, for day 5). Mechanically ventilated patients had higher neutrophil-lymphocyte ratios than non-ventilated patients during the whole follow-up period, and both of them had a trend of decrease in both patient groups (p=0.045, in mechanically ventilated patients; p<0.001, in non-ventilated patients). The comparisons of hematological parameters between mechanically ventilated and non-ventilated patients, and the time-dependent changes of parameters were tabulated in Table 2.

DISCUSSION

Organophosphorous compounds lead to many clinical effects, including hepatotoxicity, hemotoxicity, cardiotoxicity, and neurohumoral disturbances due to oxidative stress (2,12,13) Oxidative stress is defined as disturbance of balance between the production of free radicals and the antioxidant capacity of the body. Oxidative stress is the main pathophysiological mechanism of many different clinical conditions (14). In experimental and clinical studies, it has been shown that oxidative stress has an important role in acute and chronic organophosphate poisoning (15,16). If there are too many organophosphates or too few antioxidants, oxidative stress develops and causes injuries of different organ and systems (5,6,15). Also, it has been shown that the acute organophosphate toxicity is related to reactive oxygen species and lipid peroxidation (17-19). It is also shown that the increased oxidative stress contributes to increase in lipid peroxidation and decrease in phospholipids content of the membranes of the blood cell. As a result, the blood cells lose their integrity and cannot function normally (9,20-22). According to the balance between those pathophysiological mechanisms, different complete blood count results can be obtained from patients with acute organophosphate poisoning on different days of the follow-up period.

In our study, we investigated the time-dependent changes of the hematological parameters in patients with acute organophosphate poisoning. When all patients were considered, we found that patients with acute organophosphate poisoning had leukocytosis on admission to emergency department. The leukocyte counts had a trend of decrease day by day, and became nearly normal values at day 3. In studies, it was shown that the acute response of the body to organophosphate poisoning was leukocytosis, secondary to increased oxidative stress, and more severely poisoned patients had higher leukocyte counts (1,15,23,24). In our study, the results of subgroup analysis showed that mechanically ventilated patients with acute organophosphate poisoning had higher leukocyte counts. Although the leukocyte counts had a trend of decrease in each subgroup, more severely poisoned patients had higher leukocyte counts until the fifth day. According to these findings, leukocytosis seems to be a simple follow-up parameter for

organophosphate poisoning.

In our study, we found that more severely poisoned patients had higher neutrophil counts, that had same trend as the leukocyte counts. Due to a similar mechanism, the increased oxidative stress results neutrophilia in organophosphate poisonings. In experimental and clinical studies, it has been reported that neutrophilia can be seen in the early period of organophosphate poisoning (15,25,26). In the later stages of poisoning, the increased oxidative stress may lead to leukopenia and neutropenia due to increase in lipid peroxidation and decrease in phospholipids content of the leukocyte membranes (8,9). But according to our findings, leukopenia does not develop within the first five days in acute organophosphate poisoning. It can be a result of the positive balance between the antioxidant capacity of patients and the free radical formation, or a result of cessation of organophosphate exposure.

In our study, there was no difference between mechanically ventilated and non-ventilated patient groups in terms of the lymphocyte counts at day 1. Although non-ventilated patients had nearly normal lymphocyte counts during the whole follow-up period, lymphocytopenia had detected in mechanically ventilated patients after the second day of poisoning. In a study, it has been shown that organophosphate poisonings lead to lymphocytopenia due to decreased production in bone marrow (9). Also, another mechanism responsible for lymphocytopenia may be the immunotoxicity of organophosphates, and rapid destruction of lymphocytes in the circulation (7,8). According to our results, we suggest that the measured lymphocyte counts within the first 24 hours of organophosphate poisoning are not enough to estimate the prognosis.

We found that the hemoglobin levels of patients with acute organophosphate poisoning had a trend of decrease in both patient groups. The minimum values of hemoglobin levels were measured at day 3 in both groups, but mechanically ventilated patients had lower levels than non-ventilated patients from day 2 to day 5. In studies, it has been reported that anemia due to organophosphate poisoning is a well-known phenomenon (8-10). Anemia develops due to the shortened lifespan of erythrocytes and the direct inhibition of hemoglobin synthesis by organophosphates (7,20). Also, the other possible mechanisms may be decreased erythropoietin synthesis in kidneys, secondary to the renal toxicity of organophosphates, and the inhibition of acetylcholinesterase in erythrocyte membranes (7). In our study, we consider that the normal hemoglobin levels of patients with organophosphate poisoning measured within the first 24 hours were possibly due to non-depleted antioxidant capacity of erythrocytes in the early period of poisoning.

We found that there was no difference in terms of the platelet counts in both patient groups during the whole follow-up period, but there was a trend of initial decrease of platelets for three days, and then a trend of increase. In the literature, it has been reported that thrombocytopenia appears after organophosphate poisoning due to the increased oxidative stress, as seen in non-poisoning clinical conditions in which the oxidative stress is increased. (8,11). But, our results showed that the platelet counts cannot estimate the prognosis.

In recent studies it has been reported that the ratio of neutrophil and lymphocyte can also be used as an additional inflammatory marker. Neutrophil-lymphocyte ratio is a sensitive inflammatory and prognostic marker in various clinical conditions including sepsis, cardiac disorders, stroke, and acute appendicitis (27-29). In our study, we found that mechanically ventilated patients had higher neutrophil-lymphocyte ratios than non-ventilated patients during the whole follow-up period. In contrast to other hematological parameters, neutrophil-lymphocyte ratio remained higher than normal values until the fifth day of poisoning in both patient groups. In experimental studies, it has been reported that neutrophil-lymphocyte ratio increase in organophosphate poisonings, even if in subchronic, and chronic poisonings (7,11).

Limitations

This is a retrospective study, with a relatively few number of cases. We also could not objectively evaluate the reliability of the history given by the patients concerning the duration of organophosphate exposure. The prognostic value of those hematological parameters in terms of mortality should be evaluated with further prospective and large-scale clinical studies.

Conclusion

Complete blood count is performed in almost all patients with organophosphate poisoning on admission to emergency department. It results in five to ten minutes, is inexpensive and easy to interpret. It has many parameters that show the actual severity of acute organophosphate poisoning. The parameters obtained from complete blood count can be used as sensitive follow-up parameters by serial measurement.

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