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Evaluating Diagnostic Value of Electrophysiological Testing (EMG-NCV) Compared to the Activity Level of Acetylcholinesterase in Serum and Red Blood Cells of Patients with Moderate to Severe Organophosphate Poisoning

Fares Najari,[1,*] Anahita Alizadeh Ghamsari,[2] Seyyed Reza Mousavi,[3] and Bita Daadpour[2]

[1]Forensic Toxicology Specialist, Assistant Professor of Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Fellowship of Clinical Toxicology, Assistant Professor of Mashhad University of Medical Sciences, Mashhad, Iran
[3]Forensic Toxicology Specialist, Associate Professor of Mashhad University of Medical Sciences, Mashhad, Iran

[*]*Corresponding author*: Fares Najari, Assistant Professor of Shahid Beheshti University of Medical Sciences, Tehran, Iran. E-mail: FARES.HOSPITAL@yahoo.com

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Abstract

Background: Organophosphate compounds cause poisoning and death more than any other insecticide. These toxins can cause peripheral neuropathy which is delayed for about 3 - 6 weeks and no method has been known for predicting the incidence. It has been claimed that electrophysiological tests (EMG - NCV) can help in predicting the disorder.
Objectives: The main purpose of this research was to study EMG - NCV tests in patients with moderate to severe organophosphate poisoning.
Methods: This was a cross-sectional study conducted on patients with moderate to severe organophosphate poisoning from 2014 to 2016 in Imam Reza hospital of Mashhad. The minimum sample size was calculated as 68 patients and then all data was collected on the basis of inclusion and exclusion criteria using data collection form designed by the researcher, and finally data were analyzed using SPSS V.21 software, descriptive tests (including mean, median, mode) and analytical tests (K square, ANOVA).
Results: Of all 78 patients with the mean age of 27.50 $\pm$ 10.0, 45 were female and the rest were male. Totally 29.5% of the patients had abnormal EMG - NCV. Although no significant differences were observed between electro diagnostic tests (EMG - NCV) and age, gender, clinical symptoms and levels of acetylcholinesterase serum activity, the relationship between EMG - NCV and RBC levels of acetylcholinesterase activity was significant.
Conclusions: Electrophysiological tests are not associated with clinical symptoms (muscle weakness) and they cannot be considered as a determining factor to discharge the patients; therefore, careful examination of the patients or evaluating the level of AChE activity in red blood cells is needed.

Keywords: Organophosphate Poisoning, Electrophysiological Tests, Acetylcholinesterase

1. Background

Organophosphates (OP) are the most common lipophilic insecticide; they are stored in adipose tissue and cause muscarinic and nicotinic symptoms by inhibiting the acetylcholinesterase enzyme. Acetylcholinesterase (AChE) is an enzyme that hydrolyzes acetylcholine into 1- acetic acid and 2- choline substances. Acute organophosphates poisoning appears in most of the people 8 hours after exposure. These toxins can cause two types of known delayed syndromes: 1, intermediate syndrome includes weakness of proximal muscle extremities and neck flexors, paralysis of respiratory muscles and cranial nerves. The exact etiology is unknown, but one suggested theory, in this regard, is inadequate treatment or redistribution of a lipophilic compound from fat tissue. This syndrome is usually developed 24 - 96 hours after poisoning. 2, delayed peripheral neuropathy is developed 3 - 6 weeks after poisoning. Distal muscle weakness and pain are the most common symptoms (1-3). In a research conducted by De Luca C.J. et al. at Massachusetts, America in 2006, 10 - 15 mg/kg diisopropyl fluorophosphates were daily injected into the calf muscles of 4 monkeys and EMG was performed for both calves. Increasing the number of EMG led to increase in time gap that emergence of these gaps was preceded by toxicity signs (4). Another evaluation was carried out in the UK by Baker D.J. et al. in 1996. Little electromyographic changes after poisoning with organophosphates sarin were developed 3 hours and 3 days after exposure (which was 60% of its normal level of RBC AChE). These changes were not associated with any clinical signs or symptoms (5). In 1994 Shailesh K.K. et al. conducted a study on intermediate syndrome caused by organophosphate poisoning. This syndrome was developed in 38 patients of 214 poisoned patients. Electrophysiological studies were performed on 21 patients. 18 patients showed decremental response to repetitive nerve stimulation from 3 to 5 HZ with lack of post- tetanic facilitation (6). A systematic review by Karami Mohajeri and Nikfar in 2013 on EMG-NCV changes in diagnosis of organophosphate poisoning revealed that measuring

AChE is not enough for identifying subclinical abnormalities of neuromuscular transmission (NMT) and they cannot be used as a good predictive factor in this type of poisoning especially after chronic exposure to small amounts (7).

Another study that was conducted by Jalali and Balali in Mashhad from 2005 to 2006 on EMG-NCV changes in patients with moderate to severe organophosphate poisoning showed signs and symptoms of neuropathy following the improvement after the acute phase. Sensory- movement neuropathy with dominant sensory disturbance was found in 8 patients of 342 patients who underwent EMG (8).

No methods have been already known to predict these two dangerous syndromes. It can be stated that electrophysiological tests such as EMG and NCV can help to determine inhibition of AChE enzyme in nerve- muscle terminals, and also to predict this condition (9).

2. Objectives

The aim of this study was to determine the status of electrodiagnostic testing (EMG - NCV) in patients with moderate to severe organophosphate poisoning in order to predict the emergence of delayed disorders (delayed peripheral neuropathy). Meanwhile, is there a relationship between electrophysiological tests in patients with moderate to severe organophosphate poisoning and the severity of poisoning as well as activity levels of AChE in serum and red blood cells? Is there a relationship between electrodiagnostic test in patients with moderate to severe organophosphate poisoning and demographic characteristics (age and sex)?

3. Methods

Case series prospective study was carried out on all the patients with moderate to severe acute organophosphate poisoning, who referred to Imam Reza hospital of Mashhad in 2015. To increase the study's credibility, minimum sample size was calculated as 68 subjects using Bella Cohen's formula. All demographic, clinical, and paraclinical data were collected based on the data collection form developed by the researchers. Descriptive statistics (including mean, median, mode) and analytical tests (Chi-square, ANOVA) were performed using SPSS 21 software.

3.1. Inclusion Criteria

1. Confirmation of organophosphate poisoning: history of consumption, clinical symptoms, reduced level of AChE.

2. Patients with moderate to severe intoxication:

According to POP scale (Peradianiya organophosphate poisoning scale), the system determines the severity of poisoning using five clinical signs (pupil size, RR and PR, fasciculation level of consciousness). Each sign obtains 0 - 2 score, and one more score is added for those with seizures. Severe intoxication has 8 - 11 score and score of moderate poisoning is considered 7 - 4.

Based on the obtained measurements, the activity of cholinesterase in red blood cells is 30% - 50% that is equal to the average intoxication (mL-pc U/3 - 5/1), and less than 30% (less than -pc U/ mL 5/1) is considered as severe poisoning.

3. Lack of any physical illness before poisoning.

4. Over 15 years of age.

3.2. Exclusion Criteria

(1) lack of cooperation (2) consumption of other drugs simultaneously, (3) co- ingestion of pregnancy drugs, (4) addiction, and (5) patient's death.

3.3. Ethical Considerations

Before hospitalization all the patients were given written informed consent confirmed by the ethical committee. The patients were also asked to refer for EMG-NCV re-checking. Meanwhile, all data on the patients' medical record, physical examination, and interview will be remained confidential.

4. Results

Totally 78 patients (57% were female and 43% male) were included in the study. The mean age of the patients was 27.50 $\pm$ 10, average age was 26 and mode was 28 respectively (Table 1). The mean duration of hospitalization was 8 $\pm$ 3 days (average of 6 days). On initial examination, 82% of the patients had the muscular strength equal to or less than 3.5 (Table 3), and all the patients were hospitalized in ICU. A significant difference was observed between hospitalization in ICU and the severity of clinical signs (P value $<$ 0.003%). In all the patients with the muscular strength equal to or less than 2/5, the red blood cell AChE activity was lower than normal range. Although a significant difference was reported between severity of the clinical symptoms and loss of the AChE enzyme in red blood cells (P value $<$ 0/004%), the serum levels of cholinesterase in 33% of the patients were in normal range. From 34 patients admitted to ICU (43.5% of total patients), 68% had abnormal EMG-NCV within 24 hours. Although there were significant differences between the clinical severity (P value $<$ 0.003) and cholinesterase levels in red blood cells (P value $<$ 0.002), no significant difference was revealed between

the clinical symptoms and serum levels of cholinesterase (P value > 0.99). Additionally, 26 patients had normal cholinesterase level despite the severe clinical symptoms (P value > 0.2).

Table 1. Distribution of the Patients with Moderate to Severe Organophosphate Poisoning Based on the Age, Imam Reza Hospital, Mashhad

Age Groups	Frequency	Percentage
15 - 24	14	18%
25 - 34	23	30%
35 - 44	20	25%
45 - 54	13	17%
55 - 64	5	6%
65 - 74	3	4%
Total	78	100%

Table 2. Distribution of Severity of Poisoning Based on Acetylcholinesterase in Red Blood Cells in Patients with Moderate to Severe Organophosphate Poisoning, Imam Reza Hospital, Mashhad

Severity of Poisoning	Frequency	Percentage
Sever 1	68	87%
Moderate 2	10	13%
Total	78	100%

Level of AChE in red blood cells:

1. Severe 5.1 > U/mL-pc

2. Average: 3 - 5.1 pc U / mL

All 23 patients with abnormal EMG-NCV who were hospitalized in intensive care unit showed moderate to severe decrease in red blood cell AChE activity (P value < 0.05); also the EMG-NCV changes was significant in all the patients with clinical symptoms (P value < 0.001).

Atropine and pralidoxime were administered to all the patients. Although no significant difference was observed between the level of serum cholinesterase activity and the amount of used atropine and pralidoxime as well as duration of hospitalization (P value > 0.17), a significant difference was revealed between the dosage of atropine and pralidoxime and duration of hospitalization as well as the cholinesterase level in red blood cells (P value < 0.003).

Meanwhile, among all ages, decrease in level of AChE in red blood cells was not significantly different (P value > 0.2); however, by increasing the age, drop in level of serum cholinesterase enzyme was more noticeable and this difference was statistically significant (P value < 0.04). Also no significant difference was reported in changes of EMG-NCV in all ages (P value > 0.1) (Tables 2, 3, 4, 7).

Table 3. Distribution of Changes in Muscle Strength, on Admission, in Patients with Moderate to Severe Organophosphate Poisoning, Imam Reza Hospital, Mashhad

Muscle Strength	Frequency	Percentage
1.5	16	21%
2.5	27	35%
3.5	20	26%
4.5	12	15.5
5.5	2	2.5%
Total	78	100

Table 4. Results of Electrodiagnostic Testing (EMG-NCV) at Presentation in Patients with Moderate to Severe Organophosphate Poisoning, Imam Reza Hospital, Mashhad

Patients	EMG-NCV		Total
	Normal	Abnormal	
Hospitalized in ICU	11 (14%)	23 (29.5%)	34 (43.5%)
Hospitalized in general section	39 (50%)	5 (6.5%)	44 (56.5%)
Total	50 (64%)	28 (36%)	78 (100)

All 23 patients who had been admitted with abnormal EMG-NCV showed normal ranges in red blood cell levels of cholinesterase enzyme at the time of discharge (approximately 6 days later); EMG-NCV test was also performed at the time of discharge on all asymptomatic patients. However, no significant relationship was found in patients who had muscle weakness (muscular strength 4/5 to 3/5) (P value > 0.3). There was no need for the patients' follow-up after discharge but physiotherapy at home was recommended to all (Tables 5, and 6).

5. Discussion

The current study was conducted on 34 patients (43.5% of total patients) with abnormal EMG-NCV from 2014 to 2016. Although 100% of the patients had a sharp drop in acetylcholinesterase in red blood cells, acetylcholinesterase levels were within normal limits in 76% of them. No studies have instantly evaluated the relationship between these three variables so far. However, number of the patients in the current study was higher than the previous studies, and unlike other studies, the required minimum sample size has was initially calculated. No patients, in the current study, were discharged suffering from peripheral neuropathy and all of them had normal EMG-NCV that was similar to the cohort study conducted on 53 patients by Jayasingh SS et al. in Sri Lanka. Additionally, EMG- NCV was performed at discharge time and

Table 5. The Frequency of Poisoning Severity Based on Acetylcholinesterase (AChE) in Red Blood Cells and Toxicity Severity Based on the Clinical Symptoms in Patients with Moderate to Severe Organophosphate Poisoning, Imam Reza Hospital, Mashhad

Severity of Poisoning Based on the Clinical Symptoms	Poisoning Severity Based on the Level of AChE in RBC			P Value <
	Sever	Moderate	Total	
Sever	50	6	56	0.002
Moderate	18	4	22	
Total	68	10	78	

Table 6. The Frequency of Poisoning Severity Based on the Amount of Acetylcholinesterase and the Muscle Strength on Admission in Patients with Moderate to Severe Organophosphate Poisoning, Imam Reza Hospital, Mashhad

Level of AChE	The Amount of Muscle Strength on Admission						P Value <
	1.5	2.5	3.5	4.5	5.5	Total	
Sever	5	14	9	11	25	64	0.645
moderate	0	3	3	5	3	14	
Total	5	17	12	16	28	78	

Table 7. Comparison of the Prevalence of Quantitative Variables Based on the Amount of Acetylcholinesterase in Severe Toxicity in Patients with Moderate to Severe Intoxication, Imam Reza Hospital, Mashhad

	Level of AChE	Average	Standard Deviation	P Value
Age	Sever	27.5	10.45	
	Moderate	25.80	4.266	0.024
Duration of hospitalization	Sever	8	3	
	Moderate	6	3.2	0.2
Dose of atropine (mg)	Sever	125.30	154.621	
	Moderate	42.45	30.3	0.233
Dose of pralidoxime	Sever	80.214	41.878	
	Moderate	41	44.412	0.178

6 days later, EMG did not show any changes. No strong evidence of irreversible peripheral damage was also reported following acute poisoning by organophosphate (9 and 10). But in our study, a parallel connection was observed between the changes in EMG-NCV and decline in cholinesterase level in red blood cells (67.7% of the patients with abnormal EMG-NCV had a drop in cholinesterase level in red blood cells). So that by modifying the enzyme levels in red blood cells, EMG-NCV changes were also corrected at the time of registration, but the EMG-NCV changes were not significantly associated with the serum level of acetylcholinesterase. Therefore, of 34 patients, 26 ones had normal levels of acetylcholinesterase. Also in this study, both the levels of acetylcholinesterase in red blood cells and serum were reviewed. Unlike other studies that the internal level of this enzyme in red blood cells did not differ at all ages, its serum type had a significant decrease with aging while the changes of EMG-NCV at all ages were not significantly different (6, 10). In our study, no significant relationship was reported statistically between the serum level of acetylcholinesterase and muscle strength on admission, duration of hospitalization, as well as dose of atropine and pralidoxime but an association was revealed with cholinesterase level of red blood cells. Unlike the study by Jalali et al. (8), considering the normal EMG-NCV results and despite the clinical symptoms of muscle weakness at the time of discharge, it seems that this test lacks an appropriate diagnostic power to evaluate the clinical symptoms for the patient's discharge. Finally, it can be concluded that electrophysiological tests (EMG-NCV) cannot justify the muscle weakness during the days after discharge. However, no association was reported between the

tests and clinical symptoms of muscle weakness and the tests cannot be used as a determining factor for the patient's discharge. Therefore, it is suggested that discharge of patients is determined based on the clinical judgment or level of acetylcholinesterase in red blood cells or both. Meanwhile in our study, no significant correlation was observed between the serum levels of acetylcholinesterase and severity of clinical toxicity (pop scale) that was similar to the study conducted by Aygun D et al. in Turkey (6). unlike, in the current study there was a significant relationship between the levels of acetylcholinesterase (AChE) in red blood cells and poisoning severity in terms of clinical significance (pop scale) (P value < 0/004%). Due to this finding, it can be concluded that the clinical signs are more important to determine the prognosis and amounts of atropine and prolidoxime rather than serum acetylcholinesterase level.

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Footnote

Authors' Contribution: The Authors declare that they have no conflicts of interest, and they have fulfilled all the steps together.

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