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Research Paper

Prevalence of Delayed Neuropathy and Intermediate Syndrome in Acute Organophosphorus Poisoning: A Cross-sectional Toxicological/Clinical Study

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ABSTRACT

Background: Organophosphates are among the most common causes of poisoning worldwide—responsible for 3 million poisoning and 200000 deaths every year. Nearly 15% of people who are poisoned die. This cross-sectional toxicological/clinical study aimed to investigate the prevalence and influential factors in the incidence of delayed peripheral neuropathy and intermediate syndrome in acute poisoning with organophosphorus toxins. The study was conducted in Loghman Hakim Hospital, Tehran City, Iran, from 2017 to 2020.

Methods: The study data were obtained from the patients' records during follow-up. Data included demographic information (age, sex, etc.), vital signs, muscarinic, nicotinic, and neurological symptoms at admission, atropine therapy status, and pralidoxime intake status. Post-discharge complications were obtained, and patients' Electromyography (EMG) and Nerve Conduction Velocity (NCV) results were recorded and evaluated during hospitalization and follow-up. Statistical analysis was performed using SPSS software, version 22.

Results: Of 63 studied patients, 61.9% were female. The Mean±SD age of the patients was 31.90±13.128 years. Male patients were significantly (P<0.010) older than female ones. The most common muscarinic symptoms were nausea and vomiting (73.2%), diarrhea (34.92%), and abdominal pain (33.33%). Regarding the nicotinic symptoms, sweating (30.16%) and fasciculation (19.05%) were the commonest. Neurological complications were less common; seizures were observed in 3 cases (4.76%) and coma in 2 cases (3.17%). Most patients (79.4%) received pralidoxime with atropine. The Mean±SD days of treatment with atropine and pralidoxime were 5.51±3.52 and 4.06±4.62 days, respectively. Only one death was recorded. The results of the initial EMG-NCV test on the second day of hospitalization showed abnormalities in 4 patients (6.3%), indicating the presence of the intermediate syndrome.

Conclusion: The results of the EMG-NCV tests at our patients' follow-up (30 days) showed no abnormalities. Hence no cases of delayed neuropathy were seen. During hospitalization, one patient had flaccid paralysis and showed significant impairment on the EMG-NCV test (P<0.01).

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1. Introduction

Organophosphates are mainly used as insecticides; however, they are used for medical and warfare purposes, too [1]. Organophosphates are among the most common causes of poisoning worldwide [2]. There are nearly three million poisonings a year that lead to 200000 deaths. Almost 15% of people who are poisoned will die [2]. Usually, organophosphate poisoning occurs because of a suicide attempt in agricultural areas of developing countries [2]. The lung, gastrointestinal tract, and skin are the primary exposure paths [1]. Its basic mechanism of poisoning involves inhibiting the enzyme acetylcholinesterase, which leads to the accumulation of acetylcholine in the body and intoxication symptoms, such as increased saliva and tears production, diarrhea, vomiting, miosis, sweating, muscle tremors, and dizziness.

The diagnosis is usually based on symptoms and can be confirmed by measuring the red blood cell (RBC) Acetylcholinesterase (AChE) as it has been regarded as a surrogate for muscle AChE in organophosphate poisoning or measuring the activity of butyrylcholinesterase in the blood [2]. The symptoms often begin within minutes to hours after exposure; some symptoms may last for weeks [3]. To reduce intoxication cases, organophosphates with lower toxicity should be used [2]. It is also helpful to wear protective clothing while working with these chemicals and wash up afterward [4]. However, in the case of organophosphate poisoning, primary treatment should be considered, such as receiving atropine and oximes, such as pralidoxime [1]. In addition to the acute cholinergic poisoning effects, organophosphate compounds can produce an Intermediate Syndrome (IMS), OrganoPhosphate-Induced Delayed Polyneuropathy (OPIDN), and several chronic neuropsychiatric manifestations [5].

IMS was first defined by Senanayake and Karralliede [6]. It manifests within 24-96 hours after exposure when the symptoms of the acute cholinergic syndrome have nearly resolved. The syndrome is characterized by weakness of the respiratory muscles, including the intercostal muscles, diaphragm, and neck flexors, and the weakness of the proximal limb muscles and the motor cranial nerve muscles [6].

OPIDN is an unusual sequence of acute poisoning caused by some organophosphates, such as tri-orthocryl phosphate, mipafox, and leptophos. IMS generally occurs after high doses of ingested pesticides inhibit an enzymatic protein in the nervous system called neuropathy target esterase [7].

Various methods are used to diagnose IMS and OPIDN. For example, Electromyography (EMG) and Nerve Conduction Velocity (NCV) are tests that measure the electrical activity of muscles and nerves. Furthermore studies indicate that moderate to severe organophosphate poisoning increases the prevalence of neuropathy after recovery from the acute phase [8]. Because of little information about delayed peripheral neuropathy, this study aimed to investigate the prevalence and influential factors of the incidence of delayed peripheral neuropathy and IMS in acute poisoning with organophosphates. The study was conducted in Loghman Hakim Hospital, Tehran City, Iran, from 2017 to 2020.

2. Materials and Methods

Study design

In this cross-sectional toxicological/clinical study, the research information was obtained from the patients' files from 2017-2020 and their follow-up. Among all patients referred to the hospital with various types of poisoning, confirmed cases of organophosphate poisoning based on symptoms alongside measuring AChE of RBC were isolated and evaluated.

Inclusion and exclusion criteria

All patients had to be symptomatic and confirmed cases of organophosphate poisoning by the method mentioned above. These patients had to be between 20 and 55 years old without any underlying diseases.

Sample size

Based on a similar study [9], $\beta=0.2$, and $\alpha=0.05$, the sample size was determined to be 60 using the G*Power version 3.1.9.7 [10].

Data collection

Demographic and primary data (including age, sex, and so on), vital signs (including oxygen saturation, temperature, respiratory rate, and heart rate), muscarinic symptoms, nicotine symptoms, neurological complications (the categorization and definition of muscarinic, nicotinic, and neurological symptoms were the same as reported by Eddleston in 2020 [11]), Glasgow Coma Scale (GCS) score were obtained at the time of admission. Also, the atropine intake, number of days receiving pralidoxime, patients' outcomes, and post-discharge

complications were collected. All patients underwent EMG-NCV testing, and their results were recorded and evaluated during the second-day hospitalization and 30 days follow-up since OPIDN usually can be seen within 14 to 21 days after exposure [3].

Definitions of outcomes are as follows: IMS; signs and symptoms occurring after the cholinergic phase and prior to the neuropathy phase, alongside respiratory and proximal muscle weakness occurring from 2 to 4 days after the exposure [2], OPIDN; is characterized by distal axonal degeneration in both peripheral and central nervous systems occurring from 7 to 28 days after exposure (usually within weeks 2 and 3) [2], Hypertension and hypotension; in this study, systolic and diastolic blood pressure above 130 and 80 mm Hg and below 90 and 60 mm Hg were considered hypertensive and hypotensive, respectively,

Bradycardia; In this study, a heart rate below 60 beats per minute was considered bradycardia.

Ethical approval and consent to participate

The Ethics Committee of Shahid Beheshti University of Medical Sciences approved this study (ethical code: IR.SBMU.RETECH.REC.1398.833). Written informed consent was obtained from all participants. All study methods were performed in accordance with the relevant guidelines and regulations.

Statistical analysis

The study data were entered into SPSS software, version 22. First, the normal distribution of the study variables was determined by the Kolmogorov-Smirnov test. Afterward, central and dispersion indices were calculated and expressed. Depending on the distribution of variables, parametric tests such as the independent t test or nonparametric test and the Chi-square were used. The Kendall correlation test evaluated the relationship between EMG-NCV test results and muscarinic, nicotinic, and neurological symptoms. A $P<0.05$ was considered statistically significant.

3. Results

Of 63 patients with Acute Organophosphate Poisoning (AOPP), 24 (38.1%) were male, and 39 (61.9%) were female. Their Mean±SD age was 31.90±13.128 years. Also, 60.3% were between the ages of 21-41 years. The average age in male patients was significantly higher than in female patients ($P<0.05$). No cases of sinus bradycardia were observed; however, 25 patients (39.7%) had tachycardia. One case of hypotension and 15 cases of hypertension was observed. According to GCS, two patients had a GCS between 3 to 7, four had a GCS between 8 to 10, and 57 were between 11 to 13. Nine patients were intubated and needed respiratory support (14.28%). Seven cases of bradypnea and 5 cases of tachypnea and no cases of hypoxia were observed (Table 1).

The most common muscarinic symptom among patients was nausea and vomiting, prevalent in 46 cases (73.02%), diarrhea (34.92%), and abdominal pain (33.33%). The most common nicotinic symptoms were sweating, prevalent in 19 patients (30.16%), fasciculation (19.05%), and flaccid paralysis (1.59%). Seizures

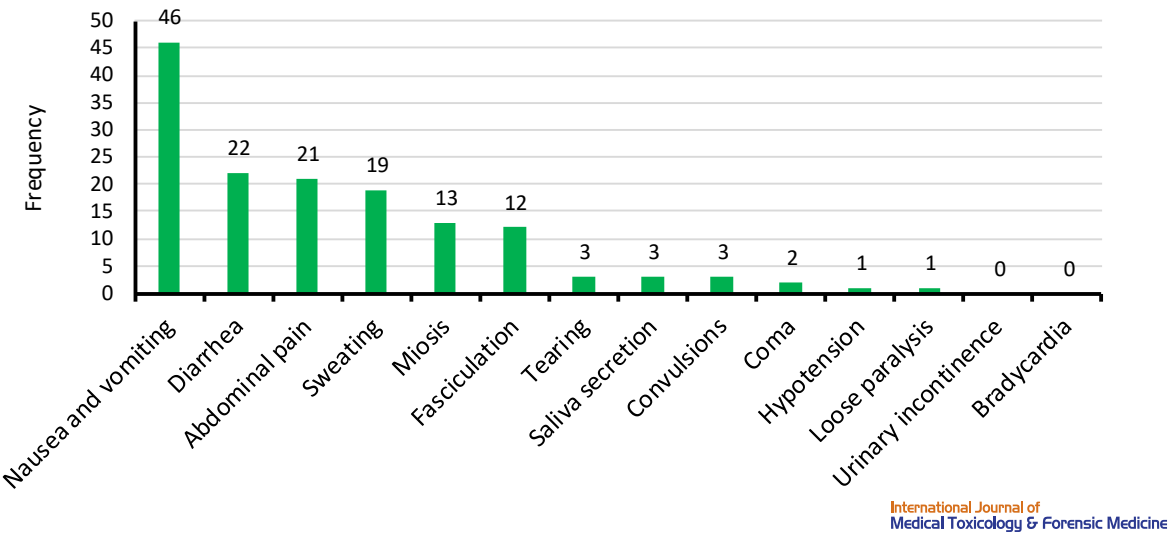

Figure 1. Prevalence of muscarinic, nicotinic, and neurological symptoms of organophosphates poisoning in patients at admission

Table 1. Information on patients with organophosphate poisoning

Variables	Mean±SD/No. (%)
Gender (male)	24(38.1)
Age (y)	31.90±13.128
Temperature (°C)	36.95±0.21
Heart rate (beat/minute)	90.51±19.997
Tachycardia	25(39.68)
Systolic blood pressure (mmHg)	116.43±12.956
Hypertension	15(23.81)
Respiratory rate (breath/minute)	17.65±8.539
Percentage of oxygen saturation	96.78±2.128
Glasgow coma scale (out of 15)	14.40±1.792
Atropine challenge test	7(11.1)
Atropine loading dose (mg)	8.468±3.71
Days of receiving atropine (d)	5.51±3.528
Receiving pralidoxime	50(79.4)
days of receiving atropine (day)	4.06±4.621
Death	1(1.59)

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were observed in 3 of the cases (4.76%) and coma in 2 patients (3.17%) (Figure 1).

The atropine challenge test was performed in 7 cases (11.1%). The Mean±SD loading dose of atropine was 8.46±3.71 mg, with a minimum of 2 mg and a maximum of 16 mg. The Mean±SD days of patients receiving atropine were 5.51±3.52 days, with a minimum of 2 days and a maximum of 16 days. Fifty patients (79.4%) received pralidoxime with Mean±SD of 4.06±4.62 days and a maximum of 30 days. Among the 63 subjects, only one fatality (1.59%) was reported (Table 2).

The results of the EMG-NCV test on the 63 patients on the second day of hospitalization showed that 4 cases (6.3%) had electrophysiological disorders suggesting the occurrence of IMS alongside facial, proximal, and neck muscle weakness. However, no abnormalities were detected in the EMG-NCV tests 30 days after discharge on 62 patients (one in-hospital fatality). According to

Table 2. EMG and NCV test results at the time of hospitalization and after discharge

Results	No. (%)	
	EMG-NCV at the Time of Hospitalization	EMG-NCV After Discharge
Disorder	4(6.3)	0
Normal	59(93.7)	47(70.01)
Not done	0	16(29.99)

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our findings, none of the patients had organophosphate-induced delayed polyneuropathy.

We found no relationship between the effect of the EMG-NCV test at the time of hospitalization and the muscarinic and neurological symptoms. The results also showed a significant relationship (P<0.001) between the result of the EMG-NCV test at the time of hospitalization (IMS) and flaccid paralysis.

4. Discussion

Acute organophosphate poisoning is one of the most common causes of poisoning referrals to the emergency department room of many hospitals. Organophosphate pesticides inhibit acetylcholinesterase and cause acetylcholine accumulation. Thus, the cholinergic nerves are overstimulated, resulting in severe cholinergic symptoms [12, 13].

In Slavica et al. study in Serbia (1998-2014), the most common clinical signs of poisoning in patients were miosis, bronchiectasis, vomiting, diarrhea, and hypotension, respectively. Acute respiratory failure was also recorded in 19.7% of the patients, and acute cardio-circulatory failure in 3.9% of patients [14]. However, in our study, the prevalence of gastrointestinal conditions was higher than miosis and bronchiectasis. The difference observed between our studies seems to result from different exposure dosages and chemicals. Luadari et al. studied the cardiovascular effects of acute organophosphate toxicity. In correlation with our study, 57 patients (49.6%) showed cardiac complications, such as sinus tachycardia. Sinus bradycardia was observed in 3 patients, hypertension in 23 patients, and pulmonary edema in 24 patients [15].

In 2010, Rastogi et al. examined neurological symptoms in the children of agricultural workers. Among 225 children, the most common reported muscarinic symptoms were salivation, tearing, and diarrhea. Clinical manifestations of nicotinic effects included excessive sweating, tremor, and mydriasis. Central nervous system symptoms such as insomnia, headache, muscle cramps, weakness, and anorexia were reported in both genders [16]. In our study, the most common muscarinic symptoms were nausea and vomiting observed in 73.02% of the patients, followed by diarrhea in 34.92%, abdominal pain in 33.33%, and miosis in 20.63%. The most common nicotinic symptoms were sweating in 30.16%, followed by fasciculation in 19.05%. Neurological symptoms were infrequent, as seizures were seen in only 4.76% of the cases and a low GCS in 3.17%.

The therapeutic dosage and treatment duration of atropine and pralidoxime depend on the severity of the symptoms. For example, in a study by Talaie et al., the Mean±SD dose of atropine bolus in patients with organophosphate poisoning was 16.4±7.9 mg, and the maximum dose was 100 mg. Atropine was given for 5.6±3.6 days. Thirty-one patients (51.7%) received pralidoxime. The Mean±SD dose of pralidoxime bolus was 1.4±0.6 g. Pralidoxime was administered for 6.3±5 days [17]. Our results showed that the Mean±SD loading dose of atropine was 8.46±3.71 mg. The average days of atropine treatment were 5.51±3.52. Fifty patients (79.4%) received pralidoxime. The average days that our patients received pralidoxime was 4.06±4.621 days.

Mortality also varies in different reports. For example, in Yurumez et al. study, the mortality rate was 9.1% [18]. Another study reported a mortality rate of 19.12% [19]. One study in Zimbabwe reported a 6.8% mortality rate due to organophosphate poisoning [20]. In our study, the mortality rate due to the poisoning was 1.59%, which is relatively low compared to other studies. This result could be due to ethnic and racial differences as well as the exposure dosage and type of organophosphate poisoning. Furthermore, taking the more invasive treatment approach and giving higher doses of antidotes may have also played a part.

A study conducted by Jalali et al. on EMG-NCV changes in patients with moderate to severe organophosphate poisoning reported a prevalence of sensory-motor neuropathy with predominant sensory impairment in 8 of 342 patients undergoing EMG [8]. Another study published by Mousavi et al. showed that electrophysiological tests are not associated with clinical symptoms (muscle weakness) and cannot be considered a determining factor in the discharge of patients [21]. In our study, there were four abnormalities in the EMG-NCV test at the time of hospitalization. No complication was observed in these patients after discharge from the hospital, and other patients showed no complications.

5. Conclusion

This study showed that the risk of delayed peripheral neuropathy after acute organophosphate poisoning is low. Although flaccid paralysis caused abnormalities on the EMG-NCV test at the time of hospitalization, it was not associated with delayed neuropathy or IMS. Moreover, the results of this study can be an excellent guide for physicians to prevent irreversible complications in patients after discharge from the hospital.

Limitations and strengths of the study

Among our limitations is the small sample size and not assessing the previous physical status of the participants prior to exposure for comparison purposes. Moreover, due to the cross-sectional nature of the study, the determination of underlying factors in IMS and OPIDN was not possible. However, despite all limitations, validated instruments were used to carry out the research.

Ethical Considerations

Compliance with ethical guidelines

The Ethics Committee of Shahid Beheshti University of Medical Sciences approved this study (Code: IR.SBMU.RETECH.REC.1398.833). Written informed consent was obtained from all participants. All study methods were performed in accordance with the relevant guidelines and regulations.

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Authors' contributions

All authors equally contributed to data gathering, analyses, preparation, and manuscript drafting.

Conflict of interest

The authors declared no conflict of interests.

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