SERUM CREATINE PHOSPHOKINASE LEVEL- AS A SEVERITY MARKER IN ACUTE ORGANOPHOSPHATE POISONING

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ABSTRACT

BACKGROUND

Organophosphorus (OP) pesticides are arguably one of the most common cause of morbidity and mortality due to poisoning worldwide especially in developing countries like India, where agriculture is the backbone of the economy. Organophosphorus pesticides poisoning can result from intentional, occupational or accidental exposure. The primary toxicity from these compounds is derived from excessive stimulation of muscarinic and nicotinic cholinergic receptors by accumulated acetylcholine in central and autonomic nervous systems as well as in skeletal neuromuscular junction. Patients with acute Organophosphorus poisoning are usually monitored by using serum acetylcholinesterase level which are expected to fall. It is not specific and does not correlate with the severity of poisoning and cannot be used as a prognostic indicator. Estimation of Creatine Phosphokinase is economical, and levels are increased both in acute as well as in intermediate syndrome and can be used as a low budget, easily available prognostic marker for acute organophosphorus poisoning.

The aim and objective of the study is to assess serum Creatine Phosphokinase (CPK) level in acute organophosphorus poisoning and to find out the correlation of serum Creatine Phosphokinase (CPK) level with the severity of organophosphorus poisoning.

MATERIALS AND METHODS

A hospital based prospective observational study was conducted on 100 patients admitted at department of medicine, Silchar Medical College & Hospital, Assam over a period of 1 year, after applying inclusion and exclusion criteria. Detailed history and clinical examination was done on each patient. Serum CPK level was measured at admission and correlation was studied with various outcome.

RESULTS

The study has shown statistically significant positive correlation between initial CPK level and severity of OP poisoning (as per POP scale) on the day of admission and atropine requirement on day 1. The cases who had higher initial CPK levels had poor outcome.

CONCLUSION

It can be inferred from this study that serum CPK level can be used as an alternative biomarker in stratifying severity of acute OP poisoning, as it is cheap, easily available.

KEYWORDS

Humans, Organophosphate Poisoning, Acetylcholinesterase, Acetylcholine, Atropine, Pesticides.

HOW TO CITE THIS ARTICLE: Das P, Bhattacharjee P, Nath BK, et al. Serum creatine phosphokinase level: As a severity marker in acute organophosphate poisoning. J. Evid. Based Med. Healthc. 2018; 5(14), 1262-1266. DOI: 10.18410/jebmh/2018/261

BACKGROUND

Organophosphorus (OP) pesticides are arguably one of the most common cause of morbidity and mortality due to poisoning worldwide especially in developing countries like India, where agriculture is the backbone of the economy.[1,2]

With increased use of compounds for agricultural and industrial purposes and due to its easy access and low cost, they are becoming a major source of health hazard. Increasing incidence of Organophosphorus poisoning is a perturbing health care challenge in developing countries, in the twenty first century.[3,4]

It is believed that between 750,000 and 3,000,000 organophosphorus poisoning occur globally every year,[5] while in India the Poison Information Centre in National Institute of Occupational Health, Ahmedabad reported that organophosphates were responsible for the maximum number of poisoning (73%) among all agricultural pesticides.[6]

Financial or Other, Competing Interest: None.
Submission 17-03-2018, Peer Review 22-03-2018,
Acceptance 29-03-2018, Published 30-03-2018.
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DOI: 10.18410/jebmh/2018/261

Organophosphorus pesticides poisoning can result from occupational, accidental or intentional exposure. Poisoning due to occupational exposure accounted for 3.6% of the incidents, accidental exposures accounted for 20.5% of the incidents and rest 75.9% incidents were suicidal.[7] Examples of organophosphates include insecticides (malathion, parathion, diazinon, fenthion, dichlorvos, chlorpyrifos, ethion, monocrotophos), nerve gases (soman, sarin, tabun, VX), ophthalmic agents (echothiophate, isoflurophate), and anthelmintics (trichlorfon). Herbicides (tribufos [DEF], merphos) are tricresyl-phosphate containing industrial chemicals.[8]

Organophosphorus insecticides are irreversible inhibitors of carboxylic ester hydrolases, including acetylcholinesterase (AChE), erythrocyte cholinesterase (EChE), plasma or butylcholinesterase (BChE) and other nonspecific proteases. The primary toxicity from these compounds is derived from excessive stimulation of muscarinic and nicotinic cholinergic receptors by accumulated acetylcholine in central and autonomic nervous systems as well as in skeletal neuromuscular junction.[9] This leads to muscarinic symptoms like bradycardia, hypotension, increased salivation/lacrimation, excessive sweating etc[10] and Nicotinic features like fasciculation, paresis or paralysis, hypertension and tachycardia.[11]

Three types of neuro muscular paralysis are noticed. Type I is due to continued depolarization at neuro-muscular junction, type II due to intermediate syndrome and type III due to delayed polyneuropathy.[12,13]

Patients with acute Organophosphorus poisoning are usually monitored by using serum acetylcholinesterase level which are expected to fall. It is not specific and does not correlate with the severity of poisoning and cannot be used as a prognostic indicator.[14,15,16] The quest for newer biomarkers in relation to OP compound poisoning started quite a long time back. It is known that serum CPK levels increases in muscle injury and is used as an indicator in muscle injury. The presence of muscle fiber necrosis in OP poisoning has already been demonstrated in animal experiments by Calore et al.[17] It has been shown that there is rhabdomyolysis in "intermediate syndrome" and consequently there is raised CPK level.[18]

Estimation of CPK is economical and levels are increased both in acute as well as in intermediate syndrome and can be used as a low budget, easily available prognostic marker for acute organophosphorus poisoning.[14,19,20]

Aims and Objectives

To assess serum Creatine Phosphokinase (CPK) level in acute organophosphorus poisoning and to find out the correlation of serum Creatine Phosphokinase (CPK) level with the severity of organophosphorus poisoning.

MATERIALS AND METHODS

A prospective observational hospital-based study was conducted in patients admitted to department of general medicine, Silchar Medical College & Hospital, Silchar with history of organophosphate compound poisoning. After getting approval from institutional ethical committee, study was conducted over period of 1 year from July 2016 to June 2017. Inclusion criteria was Patients > 13 years with history of exposure to organophosphorus compound within 24 hours (confirmation of organophosphorus compound was done by identifying the container/packet) while exclusion criteria were Other pesticide poisoning, Patients unable to show container/packet of compound consumed, Mixed poisoning, Consumption of poison with alcohol, Known medical illness like chronic liver disease, myopathy, trauma, malignancy, renal failure, autoimmune disorder, coronary artery disease, known psychiatric illness, Patients on chronic drugs like statins, steroids, fibrate, Patients who did not give consent. The eligible patients were initially subjected to Peradeniya Organophosphorus Poisoning Scale and categorized according to severity. Apart from routine laboratory investigation, serum CPK level was estimated at time of admission. Patients were followed up throughout hospital stay and various outcome noted.

The data so collected on various aspects of study were compiled, tabulated, subjected to statistical analysis in the forms of percentages. The results have been tabulated, interpreted and presented in the chapter under results and observations. Statistical analysis was performed using SPSS version 21.0. Pearson correlation test was used to derive the statistical correlation between various continuous parameters. Data were presented as mean ± standard deviation (SD). The results were considered statistically significant when the p value was< 0.05.

RESULTS

Age Group	Male		Female		Total
	N	%	N	%	
13-20	11	11	17	17	28
21-30	32	32	11	11	43
31-40	10	10	7	7	17
41-50	4	4	2	2	6
>50	5	5	1	1	6
TOTAL	**62**	**62**	**38**	**38**	**100**

Table 1. Age Distribution of Cases

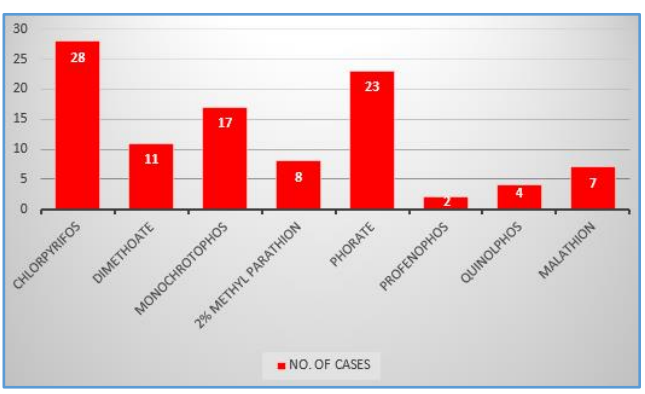

Figure 1. Distribution of Cases According to the Type of Organophosphate Compound Exposure

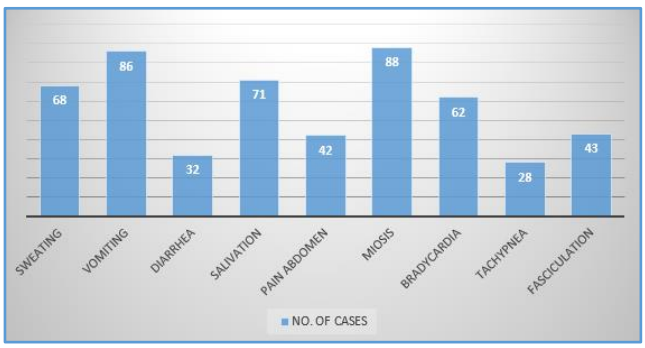

Figure 2. Distribution of Patients According to the Major Clinical Symptoms and Signs

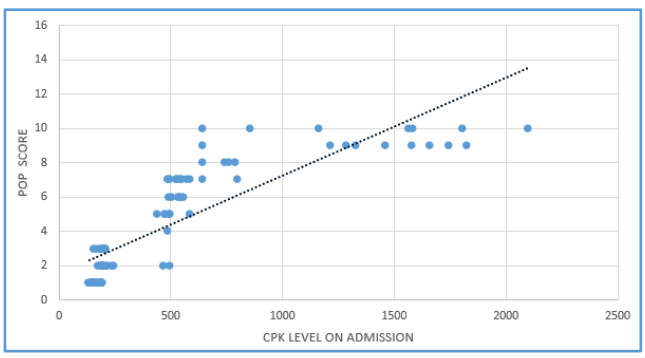

Figure 3. Scatter Plot Showing Correlation of CPK Level (IU/L) On Day of Admission with Pop Score

	CPK (Mean ± SD)	P Value
Ventilator Required		
Yes (n=18)	848.72 ± 320.1	<0.0002
No (n=82)	420.79 ± 456.72	
Intermediate Syndrome		
Yes (n=9)	913.44 ± 333.97	<0.004
No (n=91)	456.71 ± 456.31	
Outcome		
Survived(n=84)	373.79 ± 234.51	<0.00001
Expired(n=16)	1340.06 ± 466.51	
Atropine dose required on day 1(mg)		
<20	195 ± 65.52	<0.00001
20-40	538.9 ± 214.51	
>40	1308.7 ± 489.86	

Table 2. Comparison of Mean CPK Level with Different Parameter

Outcome of Cases	Initial CPK Level		P Value
	MEAN	SD	
Recovered (n = 79)	304.26	176.29	<0.00001
Intermediate syndrome-Recovered (n = 5)	860.8	413.51	
Intermediate syndrome- died (n = 4)	979.29	243.01	
Death (n = 12)	1460.33	466.42	
Total (n = 100)			

Table 3. Initial CPK Level in Various Outcomes of Cases Studied

DISCUSSION

Organophosphorus insecticides are arguably one of the most common causes of morbidity and mortality due to poisoning worldwide, especially in developing countries like India due to its easy availability.[1] The study was conducted to determine and correlate the severity of acute OP poisoning with serum Creatine phosphokinase level and also to assess the outcomes.

The present study was conducted to assess the role of serum CPK level as a severity marker in acute organophosphate poisoning cases in the Barak Valley region.

A study conducted by Dubey et al[21] had reported that 45% of patients with OP Poisoning were from age group 20-30 years and this is similar to present study where 43% of patients fall in age group of 21-30 year with mean age 28.53 ± 11.65 years (Table 1).

Other demographic profile includes male preponderance (62%) with male: female ratio being 1.63:1. Most patients were from rural area (65%) with 46% patient living below poverty line. These findings were similar to studies conducted by Bhattacharya et al,[14] Sen R et al[22] and Reddi et al.[23]

Most common mode was suicidal (88%) and most common occupation was student (30%) followed by farmer (22%) which is similar to studies conducted by Dubey et al,[21] Nermeen et al.[20]

Chlorpyrifos (28%) was most common compound (Figure 1) involved followed by Phorate (23%) which is commonly used pesticide in our area. However similar trend was noted in study of Bhattacharya et al[14] and Nagarajan et al.[24] Vomiting (86%), salivation (71%) were most common symptoms (Figure 2) while miosis (88%), bradycardia (62%) were most common sign (Figure 2) similar to study of Agrawal S et al.[19]

Creatine Phosphokinase, an enzyme which is expected to rise in patients with OP compound poisoning due to muscle necrosis. Since the half-life of CPK is about 1.5 days, it normalizes within 5 to 6 days of a single insult to the muscle. In the present study we estimated CPK level on day 1, 2, 3 and final day in hospital.

For the better assessment of CPK level as a severity marker, we correlated the value on day 1 with various parameters. (Table 2)

The present study showed that there was a high degree of correlation between the initial CPK levels and the severity of OP poisoning as illustrated by positive correlation of initial CPK with POP score (FIGURE 3). The correlation was found to be statistically significant (r= 0.847, p=<0.00001). Bhattacharya et al,[14] Nermeen et al[20] and Sen R et al[22] also reported positive correlation between the two.

In the present study, a positive correlation was observed between CPK levels and atropine required on the day of admission (r= 0.822, p= <0.00001). Bhattacharya et al[14] in their study confirmed the presence of high degree of correlation between initial CPK level and total dose of atropine in acute OP poisoning. Nermeen et al[20] also observed the similar finding.

In the present study we found a statistically significant relation between initial CPK levels and requirement of ventilatory support (TABLE 2). The patients who required ventilator support had mean CPK level 848.72 ± 320.1 on the day of admission, while other patients had mean level of 420.79 ± 456.72 ($p < 0.0002$). In the study by Dubey et al[21] no patient with normal serum CPK levels required ventilator support whereas 12 patients with elevated serum CPK levels required ventilator support ($p < 0.018$). Mural et al[25] also observed that high CPK level was associated with need for mechanical ventilation.

Out of the 100 cases, 9% developed intermediate syndrome over the course of illness (Table 2). Patient with higher CPK level developed intermediate syndrome mean value being 913.44 ± 333.97 IU/L as compared to 456.71 ± 456.31 IU/L in cases not developing intermediate syndrome. This association was statistically significant ($p < 0.004$). Out of the 9% cases who developed intermediate syndrome, 44.44% of cases (n=4) expired and others recovered eventually. In the study conducted by Nagarajan et al[24] 23.6% of cases who developed intermediate syndrome, had higher initial CPK levels as compared to those who recovered without developing intermediate syndrome.

Out of 100 cases in the present study (Table 3), 79% of the cases recovered without intermediate syndrome, 5% cases recovered after intermediate syndrome and there was 16% mortality (4% with intermediate syndrome and 12% without intermediate syndrome). Initial mean CPK level was higher in patients who died (1460.33 ± 466.42) and those who recovered with intermediate syndrome (860.8 ± 413.51) as compared to patients who recovered without intermediate syndrome (304.26 ± 176.29). This observation was found to be statistically significant ($p < 0.00001$).

Bhattacharya K et al,[14] Nagarajan et al,[24] Dubey et al,[21] Nermeen et al[20] also noted similar trend in their studies. In contrast to above finding Kumar et al[26] observed that serum CPK level was not correlated with outcome of the patients but it was statistically insignificant.

During the study period, total 16% of cases expired (Table 2). Out of which 62.5% (n=10) cases were male and 37.5% (n=6) were female. Out of 16% cases who expired 25% cases (n=4) suffered from intermediate syndrome during the course of treatment. The mean CPK level was 1460.33 ± 466.42 among the cases who expired. This trend also noted by Sen R[22] et al and Nagarajan et al[24] in their respective studies.

CONCLUSION

In the present study we found that the presentation of acute OP poisoning was more common in younger population, majority being students. The higher CPK levels on the day of admission was significantly correlated with the severity of the acute organophosphate poisoning as determined by Peradeniya OP poisoning scale. Increased CPK levels had also significant association with the need for ventilator support, atropine dose requirement and development of intermediate syndrome i.e. associated with poor outcome. It can be inferred from this study that serum CPK level can be used as an alternative biomarker in stratifying severity of acute OP poisoning, as it is cheap, easily available, especially in developing countries where acetylcholinesterase levels are not widely available.

Although, conduction of this study in a sole institution with paucity of time and resource highlighted the role of CPK level as the severity and prognostic marker in acute OP poisoning, a more elaborate multi centric study would have been desirable to precisely establish its role.

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