Original article:

Serum Creatine Phosphokinase as aMarker of Severity in Organophosphorus Compound Poisoning

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Abstract:

Background: Organophosphorous compounds are employed frequently for suicidal and homicidal purposes largely because of their easy availability at the moment of frustration and low cost. OPC poison act by inhibiting the acetylcholinesterase enzyme (AchE) at muscarinic and nicotinic receptors. Laboratory evidence of OP poisoning is usually confirmed by measuring the decreases in the blood and erythrocyte cholinesterase activities. There are emerging options for new cheaper and/or easily quantifiable biochemical markers in relation to OP poisoning like creatine phosphokinase (CPK).

Aim: To assess the CPK levels and its correlation among patients who had consumed OPC poison.

Materials and methods: A Prospective observational study was conducted on 190 patients of acute organophosphorous poisoning admitted in medicine wards and Intensive Medical Care Unit (IMCU) at Thanjavur Medical College Hospital, Thanjavur, Tamilnadu. The clinical severity was assessed and categorized according to PeradeniyaOrganophosphorous Poisoning scale. The levels of serum CPK (estimated by modified IFCC method) and plasma cholinesterase (estimated by kinetic , butrylthiocholine method) were measured on admission.

Results: The study had shown a strong positive correlation between the CPK levels and the severity of OPC poisoning. The mean CPK level in mild, moderate and severe OPC poisoning were 126, 526 and 1270 respectively.

Conclusion: Serum CPK level can be used as an alternative biomarker in diagnosis or stratifying severity of acute OP poisoning, as it is cheap, easily available, especially in developing countries where EChE and BChE levels are not widely available in most of the laboratories.

Keywords: organophosphorous poison, creatine phosphokinase, cholinesterase, acetylcholinesterase

Introduction:

Organophosphorus compound poisoning is primarily a problem of developing countries[1]. organophosphorus compound poisoning is the most common medico toxic emergency in India.Organophosphorous compounds are employed frequently for suicidal and homicidal purposes largely because of their easy availability at the moment of frustration and low cost[2]. The incidence of international organophosphorous poisoning related human exposures appears to be underestimated[3]. According to the World Health Organization (WHO) about 1 million serious unintentional poisonings occur every year and an additional 2 million people are hospitalized for suicide attempts with pesticides [4]. According to an Indian study, the incidence of OP poisoning was around 1.26 lakhs during the period of 12 months in 2007, as reported by Ravi etal[5]. The commonly encountered OP compounds comprise insecticides (including malathion, parathion, diazinon, fenthion, dichlorvos, chlorpyrifos, ethion), nerve gases (including soman, sarin, tabun, VX), ophthalmic

agents (echothiophate, isoflurophate), antihelmintics (such as trichlorfon), herbicides [including tribufos (DEF), merphos which are tricresyl phosphate containing industrial chemicals][6].

OPC poison act by inhibiting the acetylcholinesterase enzyme (AchE) at muscarinic and nicotinic receptors, producing a group of symptoms like miosis, bradycardia, increased gastrointestinal motility, emesis, sweating, tachypnea, salivation, lacrimation, altered sensorium, fasciculation, bronchospasm, blurred vision, photophobia, urination and defecation. The major complications due to OPC poisoning include acidosis, respiratory paralysis, acute renal failure, seizures, arrythmias, aspiration, coma and even death.

Furthermore, OP insecticides increase reactive oxygen species level which results in oxidative stress that contributes to cell membrane lipid peroxidation, DNA damage and cell death [7,8]. One or combination of the above mentioned complications might lead onto death. Early diagnosis is a key to cure OPC poisoning. A delay in the initiation of treatment limits the outcome and the opportunity of using 2-PAM (cholinesterase re-activator)[9].

Laboratory evidence of OP poisoning is usually confirmed by measuring the decreases in the blood and erythrocyte cholinesterase activities. However, because of wide inter-individual variability and also the cost factor the serum EChE or BChE levels are not routinely performed[10]. There are emerging options for new cheaper and/or easily quantifiable biochemical markers in relation to OP poisoning like creatine phosphokinase (CPK), lactate dehydrogenase (LDH) and serum immunoglobulins (IgG, IgA). But immunoglobulin assays, apart from being costly and difficult to perform in most laboratories and most often they become unreliable [11].

As of today only very few studies has shown that serum cholinesterase (ChE) and CPK level estimations are useful in diagnosis of organophosphorus poisoning in acute phase but it does not show any relation to the severity of poisoning [12,13]. Therefore, this study was planned to assess the correlation of serum CPK levels and their association with the severity of poisoning.

Aim: To assess the CPK levels and its correlation among patients who had consumed OPC poison.

Methodology:

A Prospective observational study was conducted in patients of acute organophosphorous poisoning admitted in medicine wards and Intensive Medical Care Unit (IMCU) at Thanjavur Medical College Hospital, Thanjavur, Tamilnadu. The study was conducted between March 2014 and Feb 2015 after getting approval from the institutional ethical committee.The informed consent was obtained from the attender of the patient's. Patients who had consumed organophosphorous compound poison without any prior treatment and got admitted to our hospital within 6 hours of consumption were included for the study. Confirmation of organophosphorous compound was done by identifying the container / packet. Patients with myopathy, chronic renal disease, epilepsy, myocardial infection, myocarditis, malignancies, autoimmune diseases and patients taking medications like statins, fibrates and dexamethasone were excluded from the study, considering the CPK levels might be elevated in those patients. A total of 190 study subjects were included for the study based on the above mentioned inclusion criteria. The clinical severity was assessed and categorized according to PeradeniyaOrganophosphorous Poisoning scale.

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The levels of serum CPK (estimated by modified IFCC method) and plasma cholinesterase (estimated by kinetic , butrylthiocholine method) were measured on admission. Blood sample was collected aseptically by a single prick after initialresuscitation, from a peripheral vein without tying any tourniquet. Patients were treated with Inj.Atropine and Inj.Pralidoxime chloride in addition to other supportive measures. Patients in need of ventilator support are intubated and mechanical ventilation given. Patients were followed up throughout the course of hospital stay. Need for ventilator support and outcome of the patient was noted.

The demographic details, clinical manifestations and the laboratory investigations were collected from all the patients and the data were entered in the SPPS version 16. Then mean and SD was derived for all the parametric variables and the pearson correlation test was used to derive the statistical correlation between the CPK levels and the severity of OPC poisoning.

Results:

The age and sex wise distribution of the entire study subjects was shown in table 1. It is seen from the table that in both the male and female groups majority of the study subjects were in the age group of between 20 – 30 years. The mean age in both males (25.43) and females (27.45) were almost similar. Of the entire study subjects males were more in numbers than the females.

Among the various poisons consumed by the study subjects chlorpyrifos (41%) and Monochrotophos (37,8%) were the most common form of OPC poison (table 2). The other forms of OPC poison consumed by the study subjects were 2% methyl parathion, dimethaote, quinolphos etc.

The severity of the OPC poisoning was assessed by PeradeniyaOrganophosphorous Poisoning (POP) scale. In that scale the following parameters were taken into consideration like pupil size, respiratory rate, heart rate, fasciculations, level of consciousness and seizures. The scoring for each parameter was between 0 – 2 and based on the final score the severity form was classified as mild: 0 – 3; moderate : 4 – 7 and severe : 8 – 11. In the presentstudy the moderate form (41%) of OPC poisoning was more common followed by mild (34.7%) and severe form (24.2%) (table 3).

The various enzymes that were measured in the patients who had consumed OPC poison were serum cholinesterase, acetyl cholinesterase, CPK and CPK-MM fraction. Table 4 shows the correlation between the various enzymes that were measured among the patients. It is inferred from the table that there was a very strong positive correlation between serum cholinesterase and acetyl cholinesterase and between CPK and CPK-MM fraction. A very strong negative correlation was established between CPK and acetyl cholinesterase.

The CPK levels can also be used in classifying the severity of OPC poisoning. In the study subjects the CPK levels were comparatively lower in the mild form of OPC poisoning when compared to the moderate and severe form (based on POP scale) and there difference in the mean was found to be statistically significant ($p<.001$). So, it proves that as the severity level increases the CPK level also increases (table 5).

The various outcome forms among the OPC poisoning patients were total recovery, intermediate syndrome – recovered, intermediate syndrome – death and death. Majority of the patients in our study had totally recovered and few others had recovered after developing the intermediate syndrome. In the present study death was reported in 21% of the study subjects. The CPK levels were much lower in the patients who had completely recovered when compared to the patients who had

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died and the difference in the levels were found to be statistically significant (p<.001). The CPK levels can be considered as a prognostic indicator in the patients who had consumed OPC poison (table 6).

Table 1: Age and sex wise distribution of the study population

Age group (in years)	Male	Female	Total
<20	15 (12.6%)	17 (23.9%)	32 (16.8%)
20 – 30	64 (53.7%)	29 (40.8%)	93 (48.9%)
31 – 40	14 (11.7%)	22 (30.9%)	36 (18.9%)
41 – 50	14 (11.7%)	3 (4.2%)	17 (8.9%)
>50	12 (10%)	0	12 (6.3%)
Total	119 (100%)	71 (100%)	190 (100%)
Mean (SD)	25.43 (5.87)	27.45 (4.32)	26.43 (6.23)

Table 2: Distribution of the study population based on the type of organophosphorous compound poison consumed

Type of Poison	No. of patients	Percentage
2% Methyl parathion	18	9.4 %
Chlorpyrifos	78	41 %
Dimethoate	6	3.1 %
Monochrotophos	72	37.8%
Profenophos	4	2.1%
Quinolphos	4	2.1 %
Triazophos	8	4.2 %
Total	190	100%

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Table 3: Distribution of the study population based on the severity of OPC poisoning by using the POP scale

Severity of OPC poisoning	Frequency	Percentage
Mild	66	34.7%
Moderate	78	41%
Severe	46	24.2%
Total	190	100%

Table 4: Correlation of various enzymes measured among the study subjects

Correlation between	Pearsons co-efficient	P value	Comments
Serum cholinesterase and acetylcholinesterase	r=0.8113	SS	High degree of positive co-relation
Serum CPK and CPK-MM fraction	r=0.9815	SS	High degree of positive co-relation
Serum CPK and Acetylcholinesterase	r=-0.7528	SS	High degree of negative correlation

Table 5: CPK levels in the various forms of severity of OPC poisoning

Severity of OPC poisoning	CPK			P value (by using ANOVA)
	Mean	SD	95% CI	
Mild	156.75	80.82	131.67 – 179.34	<.001
Moderate	526.42	185.02	467.23 – 583.56	
Severe	1269.8	500.53	1054 – 1523.54	

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Table 6: CPK levels in the various outcome forms of the study subjects

Outcome of the patient	CPK levels			P value
	Mean	SD	95% CI	
Recovered completely (n= 118)	306.56	172.54	262.54 – 356.82	<.0001
Intermediate syndrome – recovered (n= 32)	630.29	186.54	580.76 – 681.94	
Intermediate syndrome – death (n= 13)	998.62	356.21	870.43 – 1123.65	
Death (n=27)	1358.53	472.34	1105.21 – 1598.32	
Total (n=190)				

Discussions:

Organophosphorus (OP) compounds are among the most commonly used pesticides in by the farmers in their agriculture lands. Because of their wide use and easy accessibility its toxicity had become an important global health problem especially in many of the developing countries like India [14,15]. Every year, hundreds of thousands of deaths occur worldwide due to poisoning with OP compounds [16]. The symptoms of OPC poisoning are classified into muscarinic and nicotinic receptors based on the receptor involvement. Muscarinic features include excessive salivation, lacrimation, urination, diarrhea, gastrointestinal cramps, emesis, blurred vision, miosis, bradycardia, and wheezing. Nicotinic features include fasciculation, paresis or paralysis, hypertension and tachycardia. Central receptor features include anxiety, confusion, seizures, psychosis and ataxia. Three types of 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[17].

A study conducted by Weissmann-Brenner etal[18]had reported that 66% of patients with OP poisonings were males and 34% were females and it is almost in par with the present study where the males constitute 62.6% and the females constitute 37.3% of the entire study population. Majority of the patients in our study were in the third decade who would contribute to the economic status of the family and the reasons identified for consuming the poison were financial loss, family disputes, and stress and a similar type of result was quoted by a study done by Chetankumaretal[19]. In the present study Chlorpyriphos was found to be the most commonly consumed OPC poison as it is the widely used pesticide in our area and few other studies had also reported that chlorpyriphos as the most common OPC poison . There was a delay in patient reaching the hospital, which could be attributed to lack of transport facility in rural areas[19-21].

It has been shown by Senanayeke*etal*[22] that the POP score can efficiently predict the severity, morbidity and mortality of OP poisoned patients and in our study we utilised the same scoring system and we found that majority of the patients had moderate to mild severity and only 24% of the patients had severe OPC poisoning.

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In our study we found a very strong negative correlation between CPK and acetyl cholinesterase, and a strong positive correlation between serum cholinesterase and acetylcholinesterase, and between CPK and CPK-MM and the results was almost in apr with the studies done by Bhattacharya etal[21] and Nermeen etal[23]. The current study had also shown that the CPK levels are correlating with the severity of the OPC poisoning, as the severity increases the CPK levels were increasing and the CPK levels were found to be maximum in the severe form of OPC poisoning. We have observed that few patients (n=45) with IMS (intermediate syndrome) had marked elevation of CPK at baseline and required intensive care and among them 32 patients had completely recovered and only 13 patients had died. Similar findings were observed in other studies, where the serum CPK levels were more than 10,000 IU/L in moderate to severe poisoning, and they had recovered completely [24].

Our study had also proven that CPK can be utilised as a prognostic indicator in OPC poisoning, where in the patients with high CPK levels the outcome measure was found to be death and the patients with low CPK levels they had completely recovered. These findings were similar to other studies where they have tried to develop serum CPK as a tool for diagnosing the severity of OP poisoning and also as a prognostic marker for the recovery from OP poisoning [25,26].

Conclusion:

Serum CPK level can be used as an alternative biomarker in diagnosis or stratifying severity of acute OP poisoning, as it is cheap, easily available, especially in developing countries where EChE and BChE levels are not widely available in most of the laboratories. The only disadvantage in using CPK levels as a predictor is that, the other causes of elevated CPK levels should be ruled out. The serum CPK levels in acute OP poisoning can also be used as a prognostic indicator for assessing the outcome measure.One of the limitation in the present study is serial measurements of CPK was not done. To substantiate our findings more number of multicentric studies with larger sample size has to be conducted.

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