

# Study of Level of Total Serum Creatine Phosphokinase as Prognostic Indicator in Acute Organophosphorus Poisoning: A Prospective Study

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## ABSTRACT

**Introduction:** Poisoning has been found to be a major cause of death or morbidity in the developing world, the commonest being Organophosphorus (OP) poisoning. Erythrocyte cholinesterase (EchE) and pseudocholinesterase (Butyryl cholinesterase – BchE) are markers used for assessing the severity in OP poisoning, but estimation of these are costly, has variable values for different individuals and are not available at all centers. This study was done to estimate levels of serum Creatine Phosphokinase (CPK) serially in acute OP poisoning patients and to correlate with Peradeniya Organophosphorus Poisoning (POP) score to predict the prognosis.

**Material and methods:** 64 patients of acute organophosphorus poisoning admitted to S.Nijalingappa medical college and HSK hospital over a period of one year from 1<sup>st</sup> January 2015 to 31<sup>st</sup> December 2015 were taken up for the study. A brief history and detailed clinical examination was performed and patients were categorized on the basis of POP score. Level of serum cholinesterase and serum CPK were estimated at admission and CPK level was measured on day 3 and day 5. The outcome of these patients was evaluated.

**Results:** Out of 64 patients, 67% were males and 33% were females. Majority of patients were in the age group 21 – 40 years. Chlorpyrifos was the most common compound used followed by Methyl parathion. 83% had mild, 11% had moderate and 6% had severe poisoning. Serial measurements of serum CPK levels showed significant correlation with the severity of acute OP poisoning patients. The CPK levels showed a sensitivity of 70% and a specificity of 82% with a positive predictive value of 95%.

**Conclusion:** High initial serum CPK levels is associated with severe degree of poisoning and is associated with complications and mortality. CPK levels normalises by day 5 in uncomplicated cases but continues to be high in complicated cases.

**Keywords:** Creatine Phosphokinase (CPK), Organophosphorus (OP), Peradeniya Organophosphorus Poisoning (POP) Score, Pseudocholinesterase, Severity of Poisoning.

and a maximum of 24hrs in case of compounds which are highly lipophilic and which require metabolic bioactivation.<sup>6</sup> The acronym SLUDGE— salivation, lacrimation, urination, defecation, gastrointestinal distress, and emesis are often taught to associate OP poisoning. These symptoms do not usually prompt an emergency attendant to consider OP poisoning unless there is a definite history of OP exposure.<sup>7</sup>

Deaths occur due to respiratory failure occurring in one of two distinct clinical syndromes: acute cholinergic respiratory failure or the intermediate syndrome. Delayed failure appears to be due to respiratory muscle weakness, but its pathophysiology is unclear.<sup>8</sup> Patients with acute OP poisoning are usually monitored by using serum AchE 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. 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), amylase and lipase.<sup>9</sup> Estimation of CPK is easy and levels are increased both in acute phase and in intermediate syndrome due to muscle fibre necrosis. It has been reported that high serum CPK levels reflect the magnitude of acute muscle necrosis and is the best and most sensitive indicator of muscle injury.<sup>10,11</sup>

There are several systems of grading of severity in acute organophosphorus poisoning. Senanayake N<sup>17</sup> proposed Peradeniya Organophosphorus Poisoning (POP) scale for grading the severity, which is based on five cardinal manifestations of organophosphorus poisoning namely pupillary constriction, fasciculations, heart rate, respiratory rate and level of consciousness. Each sign is given a score according to the severity and all are added up to assess the severity on a 1 to 11 scale. A score of 0-3 is graded as mild, 4-7 is graded as moderate and 8-11 is graded as severe poisoning.

With increased use of compounds for agricultural and industrial purposes and due to easy access and low cost, they are becoming a major source of health hazard. So it is cardinal to recognize the

## INTRODUCTION

Poisoning has been known to be one of the leading causes of morbidity and mortality in the low and middle income countries of the world.<sup>1</sup> As it is cheap and widely available, organophosphorus (OP) compounds are most commonly used. 3 million deaths occur as a result of poisoning every year as stated by WHO.<sup>2</sup> They are used in agriculture to control pests, weeds, or plants diseases and also for suicidal purposes.<sup>3,4</sup> These compounds act by inhibiting the enzyme acetylcholinesterase (AchE) which result in accumulation of acetylcholine at muscarinic and nicotinic receptors, producing an array of symptoms principal site being the peripheral nervous system.<sup>5</sup> After ingestion, symptoms usually appear within 30-90 minutes

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entire spectrum of symptoms. Identification, risk stratification, early diagnosis and prompt treatment of OP poisoning victims are equally vital.

**Aims and objectives**

1. Clinical assessment and categorization of organophosphorus poisoning cases on admission based on Peradeniya Organophosphorus Poisoning scale.
2. To estimate the serum levels of Creatine phosphokinase in acute organophosphorus poisoning cases at admission and serially on day 3 and day 5.
3. To study correlation of Creatine phosphokinase level in acute organophosphorus poisoning based on Peradeniya Organophosphorus Poisoning scoring scale for prediction of prognosis.

**MATERIAL AND METHODS**

A hospital based prospective study was conducted on 64 patients reported and clinically diagnosed with acute OP compound poisoning admitted from casualty at S.Nijalingappa Medical college and Hanagal Sri Kumareswar hospital and research centre, Navanagar, Bagalkot from January 1st 2015 to December 31st 2015. The Ethical committee approval was obtained to carry out the study in the hospital.

**Inclusion criteria:** All cases of acute organophosphorus poisoning admitted to our hospital within 12 hours of consumption of the poison irrespective of age and sex.

**Exclusion criteria:** Patients with history of consumption of OP compound mixed with any other poison or alcohol, chronic liver disease, myopathy, malignancy, renal failure, coronary artery disease, drugs like statins, fibrates, and steroids were excluded from the study.

**Sample collection**

In all study subjects, 3 ml of plain blood was collected on admission before administration of atropine, plasma cholinesterase and serum creatine phosphokinase were estimated. Apart from serum CPK and serum cholinesterase other relevant and routine investigations were done as per need. Serum CPK was repeated on day 3 and day 5. Serum cholinesterase was estimated by colorimetric method by kit provided by Radox laboratories LTD using STAT FAX 3300 analyzer. Serum creatine phosphokinase was estimated by kit provided by BioSystems reagents and instruments using Erba Mannheim semi auto analyser.

**STATISTICAL ANALYSIS**

Data was tabulated in Microsoft excel and later SPSS V22 software and OPEN EPI version 2.3.1 was used for analysis of data. Descriptive statistics test, Kruskal Wallis test and Spearman rank correlation was used to analyse data. By using the above mentioned tests, test of significance was calculated. A P value less than 0.05 is statistically significant.

**RESULTS**

A total of 180 cases of poisoning was admitted of which 64 matched the inclusion and exclusion criteria and were studied. Regarding the age and gender distribution, our study showed that in below 20 years age group, 81.8% of cases were females and 18.2% were males. Females outnumbered males only in

under 20 age group. In 21 – 40 age group, 71.4% were males and 28.6% were females. In the age group above 41 years, all the patients were males (Table-1).

In our study, the most used compound was Chlorpyrifos (23.4%) followed by Methyl parathion (21.9%), Dichlorvos (18.8%), Monocrofos (12.5%), Quinalphos (9.4%), Malathion (7.8%), Dimethoate and Profenofos (3.1% each). Out of the fatal outcome, 2 patients consumed Dichlorvos and one each consumed Methyl parathion and Monocrofos

In our study, 53 patients (83%) were in the mild Peradeniya OP Poisoning score and had full improvement without complications, 7 patients (11%) were in moderate score and 4 patients (6%) were in the severe score. All patients who had moderate scores were intubated and put on mechanical ventilator. 4 patients who were having severe score had fatal outcome (Figure-1).

The study showed that pseudocholinesterase levels decreases with increase in severity of OP poisoning. The mean pseudocholinesterase level in mild, moderate and severe poisoning were 2389, 1104.4 and 237.5 IU/L respectively. This was found to be statistically highly significant ( $P<0.01$ ) (Table-2).

Majority of patients had full improvement without any complications in our study and these patients had lower levels of creatine kinase. The mean creatine kinase levels in different grades of poisoning on subsequent days showed higher values in

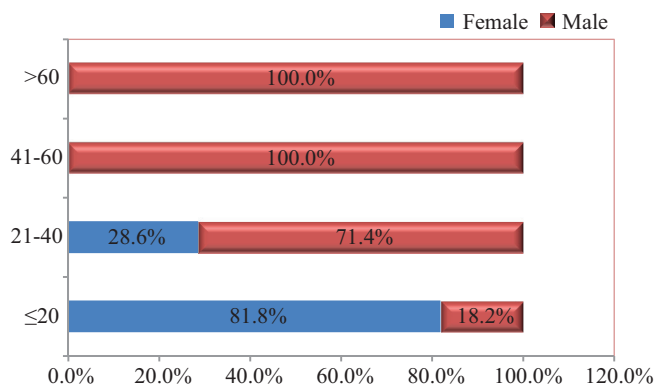
Age	Sex				Total	
	Female		Male		Count	%
	Count	%	Count	%		
≤20	9	81.8%	2	18.2%	11	100.0%
21-40	12	28.6%	30	71.4%	42	100.0%
41-60	0	0.0%	8	100.0%	8	100.0%
>60	0	0.0%	3	100.0%	3	100.0%
Total	21	32.8%	43	67.2%	64	100.0%

**Table-1:** Age and gender distribution of study population

POP score	PsCHE				
	N	Minimum	Maximum	Mean	SD
Mild	53	182	6366	2389.0	1546.9
Moderate	7	169	3462	1104.4	1384.2
Severe	4	79	490	237.5	176.5
Total	64	79	6366	2114.0	1599.9

Test applied: Kruskal wallis;  $P<0.01$ ; HS

**Table-2:** Comparison of pseudocholinesterase with pop score



**Figure-1:** Age and gender distribution of study population

patients who had respiratory depression and had to be intubated. Higher mortality was observed in patients with higher creatine kinase levels. It was found to be statistically highly significant ( $P < 0.01$ ) Figure-2, Table-3 (A, B, C).

In our study, we observed that there was high degree of correlation between initial serum creatine kinase level and severity of poisoning and those patients with high initial CPK levels had fatal outcome. Mean CPK levels were highest in the death group on all 3 days followed by those patients who survived with intubation. This was found to be statistically highly significant ( $P < 0.01$ ) Figure-3, Table-4 (A, B, C).

In our study, measurement of CPK levels shows a sensitivity of 70% and a specificity of 82% with a positive predictive value of 95% (Figure-4).

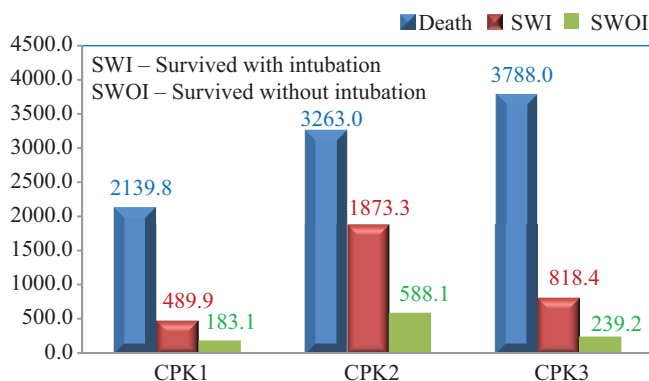
**DISCUSSION**

OP compounds are the most commonly used pesticides in agriculture. Because of their wide use and easy accessibility, poisoning with these compounds has emerged as an important health problem especially in many developing countries.<sup>12</sup>

In our study, 67% of the population were males and 33% were females. This is in consensus with a study by Bhattacharyya K

et al<sup>5</sup> at Calcutta medical college in which 66.6% were males and 33.3% were females. In a study by Hassan NAM et al<sup>9</sup> in Egypt, 48.3% were males and 51.7% were females.

Majority of patients in our study were in the age group of 21 – 40 years (65.6%) followed by below 20 years age group(17%). Females outnumbered males in the below 20 age group. This is in consensus with Bhattacharyya’s<sup>5</sup> study which showed most



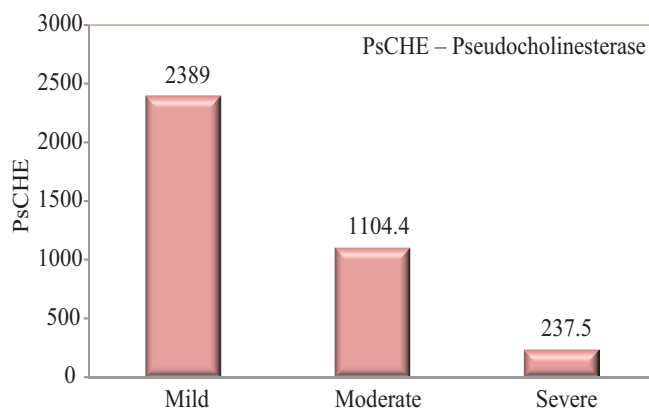
**Figure-4:** Comparison with mean CPK levels and patient outcome on day 1, 3 and 5

POP score	CPK on day 1				
	N	Minimum	Maximum	Mean	SD
Mild	53	91	352	183.1	65.9
Moderate	7	366	547	489.9	76.0
Severe	4	1960	2324	2139.8	149.1
Total	64	91	2324	339.0	483.8
Test applied: Kruskal wallis; $P < 0.01$ ; HS					
POP score	CPK on day 3				
	N	Minimum	Maximum	Mean	SD
Mild	53	194	2170	588.1	382.1
Moderate	7	996	2670	1873.3	731.0
Severe	2	2962	3564	3263.0	425.7
Total	62	194	3564	819.5	741.4
Test applied: Kruskal wallis; $P < 0.01$ ; HS					
POP score	CPK on day 5				
	N	Minimum	Maximum	Mean	SD
Mild	53	76	872	239.2	150.6
Moderate	7	480	1181	818.4	226.4
Severe	1	3788	3788	3788.0	
Total	61	76	3788	363.9	507.9
Test applied: Kruskal wallis; $P < 0.01$ ; HS					

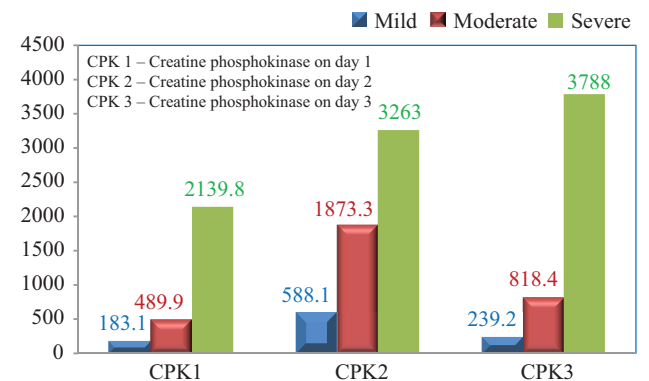
**Table-3 (A,B,C):** comparison of mean cpk level in different grades

Outcome	CPK on day 1				
	N	Min	Max	Mean	SD
Death	4	1960	2324	2139.8	149.1
SWI	7	366	547	489.9	76.0
SWOI	53	91	352	183.1	65.9
Total	64	91	2324	339.0	483.8
Test applied: Kruskal wallis; $P < 0.01$ ; HS					
Outcome	CPK on day 3				
	N	Min	Max	Mean	SD
Death	2	2962	3564	3263.0	425.7
SWI	7	996	2670	1873.3	731.0
SWOI	53	194	2170	588.1	382.1
Total	62	194	3564	819.5	741.4
Test applied: Kruskal wallis; $P < 0.01$ ; HS					
Outcome	CPK on day 5				
	N	Min	Max	Mean	SD
Death	1	3788	3788	3788.0	
SWI	7	480	1181	818.4	226.4
SWOI	53	76	872	239.2	150.6
Total	61	76	3788	363.9	507.9
Test applied: Kruskal wallis; $P < 0.01$ ; HS					

**Table-4 (A,B,C):** Comparison with mean cpk levels and patient



**Figure-2:** Comparison of pseudocholinesterase with pop score



**Figure-3:** Comparison of mean CPK level in different grades of poisoning on day 1, 3 and 5

patients in the age group of 21 – 30 years. But Narmeen's<sup>9</sup> study reported 11 – 20 as the commonest age group.

Chlorpyrifos (23.4%) was the most commonly used compound followed by Methyl parathion (21.9%) and Dichlorvos (18.8%). In a study by Chethan Kumar et al<sup>13</sup> at Sri Deveraj Urs Medical college, Kolar, the most commonly used compound was Chlorpyrifos followed by Methyl parathion. In Narmeen's<sup>9</sup> study, the commonest compound was Malathion. Currently the majority of deaths in Sri Lanka are due to class II OP compounds, in particular the dimethyl OPs fenthion and dimethoate.<sup>14</sup> Most frequently reported pesticides in America are chlorpyrifos, etoprophos, methamidophos, methyl parathion, monocrotophos and terbufos.<sup>15</sup>

100% of cases in our study were suicidal in nature and the route of exposure was oral. The most common route of exposure was oral route (73.3%), most common manner of poisoning was suicidal (56.7%) in Narmeen's study.<sup>9</sup> Weissmann-Brenner et al<sup>16</sup> reported that 64% of cases had accidental exposure and 36% were suicidal, the most common route was oral (67%). In developed countries, commonest manner of poisoning is accidental and in developing countries, it is suicidal.

It has been shown by Senanayeke et al<sup>17</sup> that POP score can efficiently predict the severity, morbidity and mortality of OP poisoned patients. 53 out of 64 (83%), 7 out of 64 (11%) and 4 out of 64 (6%) were considered as mild moderate and severe cases of poisoning in our study.

The mean pseudocholinesterase levels were 2389, 1104.4, 237.5 (IU/L) in mild, moderate and severe cases of poisoning in our study. In Narmeen's<sup>9</sup> study, the mean pseudocholinesterase levels were 5834.8, 2077.2, 607.4 (IU/L) in mild, moderate and severe cases of poisoning. In Bhattacharyya's<sup>5</sup> study, they measured Erythrocyte cholinesterase (EchE) levels and they were found to be 8783.53, 4770.19 and 2021.93 (IU/L) in mild, moderate and severe cases of poisoning. EchE level estimation is not done in our hospital.

The mean CPK levels on day 1 were 183.1, 489.9 (IU/L) in mild and moderate cases of poisoning in our study. Mean CPK levels were 273.53, 456.06, 1032.57 (IU/L) and 89.1, 273 and 688.8 (IU/L) in Bhattacharyya and Narmeen's study respectively. Mean CPK was found to be elevated (2139.8 IU/L) in fatal cases. These results are in consensus with Bhattacharyya et al.

The present study showed that there was a high degree of correlation between the initial serum CPK levels and the severity of OP poisoning as illustrated by the positive correlation of initial CPK with POP score and the negative correlation of initial serum CPK with Pseudo cholinesterase. These correlations are found to be statistically significant ( $p < 0.001$ ). Bhattacharyya et al<sup>5</sup>, Narmeen et al<sup>9</sup> and Sen R et al<sup>18</sup> reported that there is a high degree of correlation between initial CPK levels and the severity of poisoning. This is further supported by D. Markandeyulu's<sup>19</sup> and Kumar et al's<sup>13</sup> study. Counselman et al<sup>20</sup> stated that CPK levels peak within 24 to 48 hours of the onset of muscle injury or rhabdomyolysis and then decline at a relatively constant rate of 39% of the previous day's value. Sahjian and Frakes<sup>21</sup> stated that if there is ongoing injury to the muscle due to development of complications, the CPK level continues to be elevated. Since half-life of CPK is about 1.5 days, it normalises within 5 to 6 days of a single insult to the muscle.

It is known that serum CPK levels increases in muscle injury

and is used as an indicator in muscle injury. High serum CPK activity shows the magnitude of acute muscle necrosis. The presence of muscle fiber necrosis in OP poisoning has already been demonstrated in animal experiments by Calore et al.<sup>22</sup> It is also measured to determine the course of muscle injury.

John et al<sup>11</sup> and Chetan Kumar G et al<sup>13</sup> concluded that muscle damage determines the subsequent development and severity of intermediate syndrome. In our study, we observed that serum CPK level is elevated even in the absence of intermediate syndrome, provided the patient is severely poisoned. Studies by Dursun Aygun et al<sup>10</sup> and Karalliedde et al<sup>23</sup> also reported the same.

In our study, we found that high initial CPK level is associated with need for endotracheal intubation and mechanical ventilation and more chances of mortality. We observed that mean CPK levels was highest in death group on all 3 days followed by patients who survived with intubation. Mean CPK levels had come down to around 200 IU/L in the first group whereas it was still elevated in the intubated patients and in those who died. In death group, mean CPK level was 2800 IU/L. Dayanand Raddi<sup>24</sup> et al reported that the elevation of CPK levels is predictive of subsequent respiratory failure. Sen R et al<sup>18</sup> and Sumathi et al<sup>4</sup> also reported the same.

In our study, we found that high initial serum CPK levels is associated with severe degree of poisoning and is associated with complications and mortality. We also found that CPK levels normalises by day 5 in uncomplicated cases but continues to be high in complicated cases. The results were statistically significant ( $P < 0.001$ ).

## CONCLUSION

In conclusion, this study found that Serum CPK can be used as an alternative biomarker in diagnosis or stratifying severity of acute OP poisoning, as it is cheap and easily available, especially in developing countries. Serial measurements of serum CPK levels in acute OP poisoning can predict the prognosis.

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