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Creatine Phosphokinase: A Prognostic Marker in Organophosphorus Compound Poisoning

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Abstract
Background: *In developing countries like India, organophosphorus compounds (OPC) constitutes for 80% of pesticide poisoning. Creatine phosphokinase (CPK) is emerging recently as a prognostic marker in OPC poisnoning. This study is done to analyse the clinical utility of CPK in OPC poisoning patients.*
Aim: *To estimate Serum CPK levels in patients who have consumed Organophosphorous compound (OPC) poisoning and to assess the role of Serum CPK (CPK) as a marker of severity and correlate it withthe incidence of respiratory failure and final outcome in OPC poisoning.*
Materials and Methods: *50 patients of acute OPC poisoning, aged 14 years and above, admitted in Rajah Muthiah medical college and hospital, within 6 hours of exposure irrespective of route of exposure and sex were selected and subjected for study. They were assessed clinically on admission by Peradeniya OPC Poisoning scales and categorized according to the severity. Then, they were also subjected to estimation of serum CPK at the time of admission and 48 hours after admission.*
Results: *CPK values were increased among 60% of study group at 0 hours and 68% at 48 hours. There was a significant increase in serum CPK levels from 0 to 48 hours which is of high statistical significance (p =0.001).*
Conclusion: *The correlations of serum CPK with outcomes such as ventilatory function and survival of the patient were statistically significant and positive at both periods of measurement. Therefore, serum CPK measurement is not only crucial at 0 hours, it is equally important to have serial monitoring of serum CPK levels, which ultimately tells the prognosis of the patients.*
Keywords: *organophosphorus compound poisoning, Creatine phosphokinase (CPK), Prognosis.*

Introduction

Pesticides have both acute and chronic health hazards upon exposure either by occupational activity or by self- harm as labour-intensive agriculture is considered as the major component of Indian economy. Ravi et al described the incidence of organophosphorus compound (OPC) poisoning as around 1.26 lakhs during the year 2007 in India. About 92,000 deaths were due to OPC poisoning in the year 2010[(1)]. The enzyme acetylcholinesterase (AchE), responsible for the metabolism of acetyl choline, is inhibited by OPC

compounds. This causes accumulation of acetylcholine at muscarinic and nicotinic receptors producing cholinergic symptoms depending on the site of action[(2)].

Symptoms appear within 30-90 minutes of exposure and may be as late as 24hours in highly lipophilic compounds[(3)]. The muscarinic symptoms go by the acronym SLUDGE-salivation, lacrimation, urination, defecation, gastrointestinal distress, and emesis[(4)]. The nicotinic action produces muscle twitching, fasciculation and respiratory muscle paralysis[(5)].

Death in OPC poisoning is mostly due to respiratory paralysis, which can occur in either acute cholinergic crisis phase or during intermediate syndrome[(6)]. Hence early recognition and prompt ventilatory support may improve survival of the patients.Evidence based management protocols and research tool are lacking in the management of acute OPC poisoning. Therefore, this study is designed to assess if serum creatine phosphokinase (CPK) can be used as biomarker of severity in OPC poisoning and as a prognostic tool.

The present study was conducted with an objective to estimate Serum CPK levels in patients who have consumed OPC and to correlate it with need for ventilatory support and survival in OPC poisoning.

Materials and Methods

This is a prospective observational study conducted among patients of acute OPC poisoning admitted to Rajah Muthiah Medical College and Hospital during the period of November 2016 to September 2018. After getting institutional ethical committee clearance and an informed consent from the patient or their attenders, 50 cases of acute OPC poisoning of both sexes, aged 14 years and above, having an exposure within 6 hours irrespective of mode of exposure were selected and subjected for the study.

Exclusion Criteria

- Patient less than 14 years of age
- Patient with history of mixed poisoning
- Patient with history of trauma
- Patients who had undergone cardiopulmonary resuscitation
- Known case of coronary artery disease, chronic kidney disease, epilepsy, psychiatric illness, sepsis, myopathy
- Patient who have been administered IM injection in the past 24 hours
- Patient on medications like statins, fibrates, aspirin, diuretics and steroids

They were assessed clinically on admission by Peradeniya OPC Poisoning scales and categorized according to the severity. They were subjected to routine blood investigations like blood sugar, blood urea, serum creatinine, serum acetylcholinesterase and ECG. They were also subjected to estimation of serum CPK at the time of admission and 48 hours after admission. Serum CPK was measured using NAC activated kinetic method. Patients were treated according to our hospital protocol with atropine, pralidoxime, other supportive measures and mechanical ventilation, if needed. Clinical course and outcome of the patients were noted. All the collected datas were analysized by Statistical Package of Social Sciences (SPSS) 21 software.

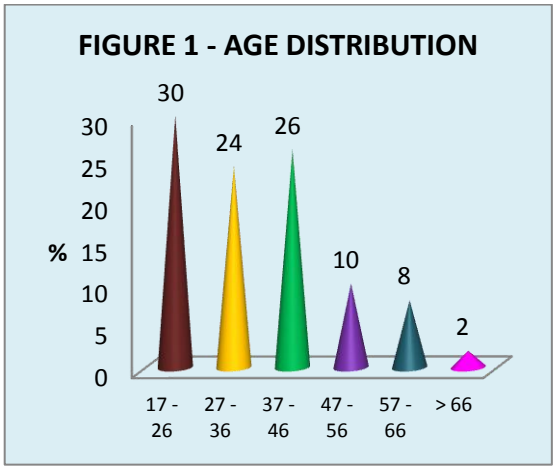
Table 1 The Peradeniya OPC Poisoning scale

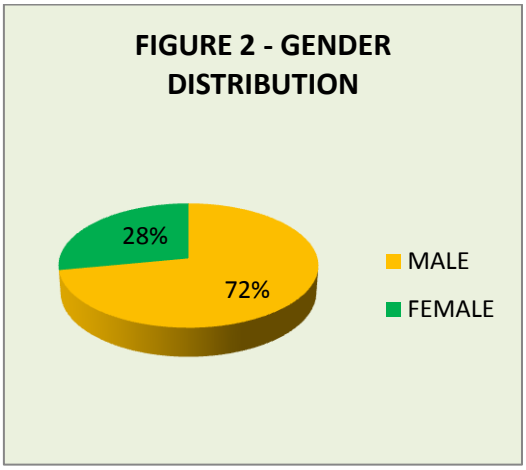
Parameters	Criteria	Score
Pupil size	>2mm	0
	<2mm	1
	Pin point	2
Respiratory rate	<20/min	0
	>20/min	1
	>20/min with central cyanosis	2
Heart rate	>60/min	0
	41 – 60/min	1
	<40/min	2
Fasciculation	None	0
	Present, generalized / continuous	1
	Both generalized and continuous	2
Level of Consciousness	Conscious and rationale	0
	Impaired response to verbal commands	1
	No response to verbal commands	2
Seizures	Absent	0
	Present	1

Note: 0 – 3 Mild Poisoning; 4 – 7 moderate poisoning; 8 – 11 severe poisoning

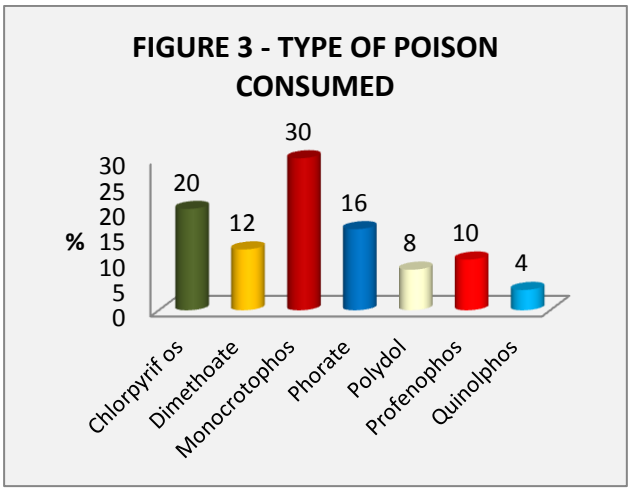
Results

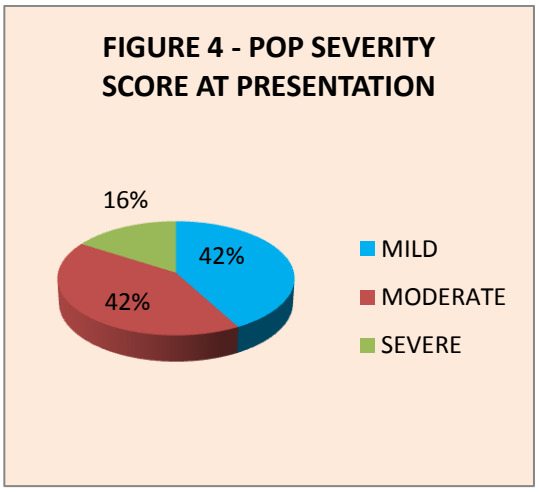
In the present study, the mean age was found to be 36.66± 14.15 years. Most of the study population were in the age group of 17–26 years (N=15, 30%) and 37–46 years (N=13, 26%). Males predominated the group comprising 72% of the total study population. (Figure 1, 2).





Monocrotophos (N=15, 30%) was the most common poison consumed in the present study, followed by chlorpyrifos (N= 10, 20%). (Figure 3) Most patients in this study presented with mild (N=21, 42%) and moderate POP severity (N=21, 42%). Only few patients (N=8, 16%) had severe POP score at the time of presentation. (Figure 4)





The serum CPK value was found increased in 60% of patients at the time of presentation. Increase in CPK was observed in 68% of patients after 48hours of consumption. (Table 2)

Table 2 - CPK Distribution at 0 Hours and 48 Hours

Serum CPK	CPK At '0' Hours		CPK After '48'hours	
	No. of Patients	Percentage (%)	No. of Patients	Percentage (%)
Normal	20	40	16	32
Increased	30	60	34	68
Total	50	100	50	100

The mean CPK value at the time of presentation was 464.64±381.97 IU/L and at 48 hours was 898.06±1134.01 IU/L (Figure 5). The repeated measures ANOVA proved that measured CPK values were statistically significant (p=0.002) (Table 3).

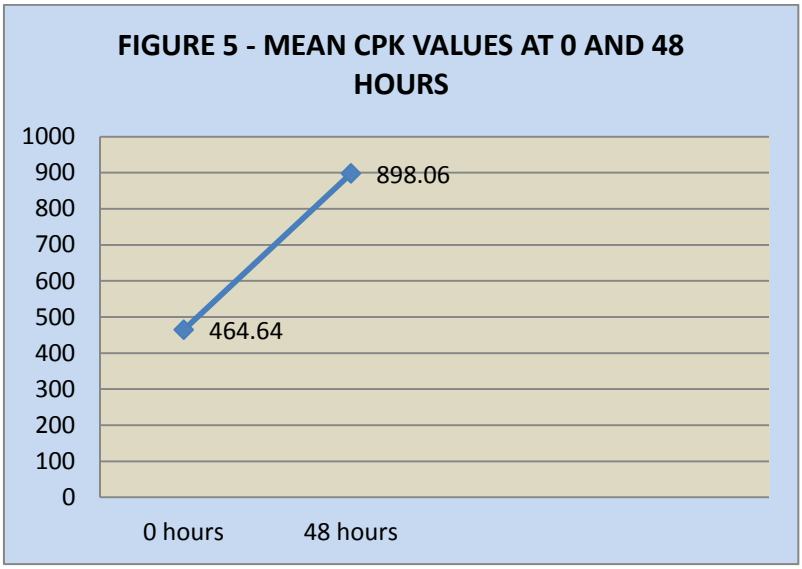


Table 3 – Pair wise Comparison of CPK Values by Anova			
Serum Cpk Pairwise Comparison		**Mean Difference**	**P**
CPK 0 HOURS	CPK 48 HOURS	-433.42	**0.002**

Table 4 Correlation of Serum CPK Values and Difference in CPK with Ventilatory Support and Outcome of the Patient – Using Spearman's Correlation

Outcomes	**CPK At '0' Hours**		**CPK After '48'hours**		**CPK '0' Hours To '48' Hours**	
	Value	**P**	**Value**	**P**	**Value**	**P**
Ventilatory Support	0.543	**0.001**	0.713	**0.001**	0.697	**0.001**
Death	0.597	**0.001**	0.589	**0.001**	0.525	**0.001**

The correlations of serum CPK values at 0 hours and 48 hours with outcomes such as ventilatory support and survival of the patient were statistically significant and positive at all both the periods of measurement. To further strengthen the present work, the difference in CPK values between 0 to 48 hours were correlated with study outcomes. There was a significant increase in serum CPK levels from 0 to 48 hours (Table – 4) and interestingly, the difference had a high level of statistical significance (p = 0.001).

Discussion

The initial rise of serum CPK in OPC poisoning is probably due to the presence of muscle fiber necrosis. This has been demonstrated in two patients by Kuntal Bhattacharyya et al[(2)]. Yves Vanneste & Dominique Lisson had shown that rhabdomyonecrosis occurs after OPC poisoning and was accompanied by a concurrent increase in serum total CPK activity[(7)]. In our study, 60% of patients had high serum CPK levels at the time of admission, which increased further to 68% after 48 hours.

The mean CPK levels at 0 hours and 48 hours were 464.64 and 898.06 (IU/L) in our study. Mean CPK levels were 456.06, 1032.57 (IU/L) and 273 and 688.8 (IU/L) in Bhattacharyya and Nermeen's study respectively[(8).] The correlation between initial CPK levels and poison severity was reported by Bhattacharyya et al, Nermeen et al and Sen R et al[(2,9,10)]. Similar result was also obtained in studies conducted by D. Markandeyulu et al and Kumar et al[(11)] study. It also correlated with the incidence of need for ventilator support and outcome.

In a study by Senanayeke et al[(12)], POP score was proved to be efficient to assess the severity, morbidity and mortality of OP poisoned patients. On applying POP score in the this study, we found 42% were in mildseverity and found 42% were in moderate severity respectively and only 16 % had

severe POP score.1 ventilated patient with mild POP severity and 5 ventilated patients with moderate POP severity had rising levels of serum CPK.

Counselman et al[13] 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. A study conducted by M. John, A. Oommen, A. Zachariah in Christian Medical College Vellore proved that muscle injury begins in all patients with OPC poisoning at the time of admission, attains peak overfirst 5 days and starts to declineover the next 5 days[14]. Animal experiments by Calore et al.[15] demonstrated muscle fibre necrosis in OP poisoning. The mean half-life of CPK is about 1.5 days. Sahjian and Frakes[16] stated that if there is ongoing injury to the muscle due to development of complications, the CPK level continues to be elevated. The increased muscle injury warrants increased the need for early ventilator care. Thus, keeping the half life of CPK in view, a repeat measurement of CPK level after 48 hours will help in early identification of ongoing muscle injury, need for early ventilator care and improves the prognosis. In the present study, the correlations between serum CPK levels at '0' hours and 48 hours of admission showed a high degree of positive correlation with ventilator support and outcome of the patient (r=0.697, 0.567, 0.439 and 0.525). These correlations were also statistically significant (p=0.001).

Hence, it is necessary for estimating CPK levels, especially after 48 hours, so that complications can be recognized at the earliest and patients can be immediately managed, reducing morbidity and mortality.

Conclusion

Serum CPK measurement should be measured at the time of presentation. It is equally important to have serial monitoring of serum CPK levels, which ultimately tells the prognosis of the patients. At least, two values of CPK at 0 hours and 48 hours should be taken and it can be used as a parameter for assessing the severity and outcome of acute OPC poisoning. Thus increase in CPK at 48 hours can serves as an alarming signal for respiratory failure and death, necessitating intensive monitoring and ventilatory support to improve the survival of the patients.

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