ISSN- O: 2458 - 868X, ISSN–P: 2458 – 8687
Index Copernicus Value: 68 . 16
PubMed - National Library of Medicine - ID: 101731606

International Journal of Medical Science and Innovative Research (IJMSIR)
IJMSIR : A Medical Publication Hub
Available Online at: www.ijmsir.com
Volume – 4, Issue – 4, July - 2019, Page No. : 106 - 112

Study of prognostic significance of serum levels of creatine kinase in Organophosphorus poisoning cases

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Type of Publication: Original Research Paper

Conflicts of Interest: Nil

Abstract

Introduction: Organophosphorus poisoning is wildly used insecticide in developing country like India because of its easy availability. Organophosphorus compound poisoning being very common poisoning causing high mortality rate. Various clinical markers can be relevant in evaluation of the patients but the role of serum enzymes such as creatine kinase have been studied with many contradictory reports in the literature, which led us to plan this study to understand the prognostic significance of serum creatinine kinase in the patients of OP poisoning and their correlation with the outcomes. Material and **Methods:** we conducted a prospective study in 100 patients of OP poisoning who were followed up from admission to discharge or death. Serum creatine kinase analyzed to find their relationship with outcome parameters such as total dose of atropine needed until final outcome, requirement of mechanical ventilation, total hospital stay.

Results: The patients had a mean age of 32.4 ± 13.5 years with male to female gender ratio of approximately 5. Study population had mean hospital stay duration of 5.5 ± 3.49 days. The overall mortality was 21%. Mortality of patients with raised serum creatine kinase was significantly higher (0.039) than the patient with normal levels Patients who had raised creatine kinase levels had significantly higher mortality, hospital stay, total atropine dose and necessity for mechanical ventilation.

Conclusion: Serum creatine kinase is raised in almost one third of the patients of organophosphorus poisoning and its baseline level could help in predicting the outcomes in terms of atropine dose required, hospital stay, mortality. We recommend Creatine kinase levels as alternate prognostic biomarkers in Organophosphorus poisoning.

Introduction

Organophosphorus (OP) compounds are insecticides which are widely used in agriculture to control pests, weeds, or plants diseases. It was a German scientist, Schrader [1], whose initial research led to the future development of over 2000 organophosphorus (OP) compounds, including tabun, tetraethyl pyrophosphate, Diethyl phosphate and sarin. Organophosphorus compound poisoning is an important preventable public health problem in developing countries [2]. Organophosphorus compounds are responsible for a majority of suicidal attempt in India due to its easy availability. The OP compounds act by inhibiting acetylcholine esterase enzyme at nerve endings and neuromuscular junction, causing overstimulation of acetylcholine receptors. Signs and symptoms of poisoning

are mainly due to muscarinic, nicotinic and central nervous system (CNS) receptor over-stimulation [3]. These include bradycardia, hypotension (Muscarinic), increased salivation/lacrimation, excessive sweating, nausea, vomiting, diarrhea, pain abdomen, fecal and urinary incontinence. CNS manifestations include anxiety, restlessness, convulsion, miosis, insomnia, coma, cheyne-stokes breathing, respiratory and cardiovascular failure.

In acute OP poisoning, laboratory evaluation plays an important and crucial role for confirmation of poisoning, diagnosing the first acute organ damage and assessing the severity of poisoning. In laboratory assessment of OP poisoning, estimation of plasma cholinesterase is most specific test for OP poisoning. Apart from few case reports, very few studies were conducted till date to evaluate the effect of organophosphorus compounds on enzymes like creatine kinase.

Creatine kinase (CK)—also known as creatine phosphokinase (CPK) or phospho-creatine kinase—is an enzyme expressed by various tissues and cell types. CK catalyse the conversion of creatine and utilizes adenosine triphosphate (ATP) to create phosphocreatine (PCr) and adenosine diphosphate (ADP). This CK enzyme reaction is reversible and thus ATP can be generated from PCr and ADP [4]. Tissues and Cells consume ATP rapidly. PCr serves as an energy reservoir for the rapid buffering and regeneration of ATP in situ, as well as for intracellular energy transport by the PCr shuttle or circuit [5]. It was also documented that there is rhabdomyolysis in “intermediate syndrome” and followed by a proportionate raise in CPK level [6]. Intermediate syndrome (type 2 paralysis described by Senanayake [7]) occurs 24–96 h after poisoning with organophosphorus compounds, following the acute stage of cholinergic crisis. The creatine kinase could be an important enzyme which can help in identifying this pathology in patients with OP poisoning. With this background, we conducted this study in the patients of OP poisoning to understand the prognostic significance of creatine kinase.

Methods

A prospective observational study at a tertiary healthcare hospital. The study was conducted after formal approval from institutional ethics committee and conducted in compliance with ICH-GCP guidelines. The study was conducted with the 100 patients of OP poisoning including Diagnosed cases of OPC poisoning admitting to the hospital ward (General or ICU) with informed consent excluding Patients with history of exposure to a poison other than organophosphorus compounds and mixed poisoning ,Patients of chronic liver disease, Clinical history suggestive of myopathy, Patients with history of malignancy and autoimmune diseases, Patients with history of ischemic heart disease, History of intake of hepato-toxic drugs like,–Statins, Fibrates , steroids , phenytoin , isoniazid , anti-retro viral drugs like nevirapine within previous 30 days of admission.

The demographic features of the patient were recorded which included age, gender and date of admission and date of poison consumption. The vital parameters of the patient including blood pressure, heart rate and respiratory rate were recorded. Patients underwent the treatment as per the standard hospital and emergency protocols (with atropine 3–5 ml (0.6 mg/ml) bolus followed by continuous infusion with titration based on clinical assessment, and pralidoxime 2 g bolus over 30 min followed by 1 g/h for 48 h.) Serum creatine kinase activity starts to increase after 6 hours and lasts up to 5-6 days. The peak levels are existent after a period of 24 hours [8]. Thus, the laboratory investigations were performed at 48 hours after the patient’s consumption of poison. The creatine kinase was

measured by spectrophotometric methods [9]. Serum pseudocholinesterase level was estimated at the time of admission in all the patients by DGKC method (LiquiChek). The total dose of atropine (mg) until the final clinical outcome (complete recovery or death) was calculated for each patient. The requirement of mechanical ventilation, total hospital stay duration were recorded. Chi Square test was performed for the comparison of proportions between two groups. Unpaired t test was used for comparison of parametric variables between the two groups. For correlation analysis of enzyme levels with outcome parameters, coefficient of correlation (Pearson's) was calculated. The strength of correlation was decided based on correlation coefficient as : >0.75 : Strong , 0.5 to 0.75: Moderate ,0.25 to 0.5: Mild. A p value of less than 0.05 was considered significant. The data entry was processed in Microsoft Excel 2013 version and all the statistical analysis was performed in IBM SPSS software version 13.

Results

We enrolled a total of 100 patients of OP poisoning after reviewing their study eligibility criteria. The baseline demographic features of them are described in the table below:-

Feature	Observation
Total patients	100
Male	84(84%)
Female	16 (16%)
Mean Age	32.4 ± 13.5 years
Mean age Male	29.9 ± 12.2 years
Mean Age Female	36.7 ± 15.4 years
Intake Cause:	
Intentional	98 (98%)
Accidental	2 (2%)

Table 1: Baseline Demographic Features of the Study Population

In the total population, 84% were male patients while 16% were female patients as depicted in the figure below.

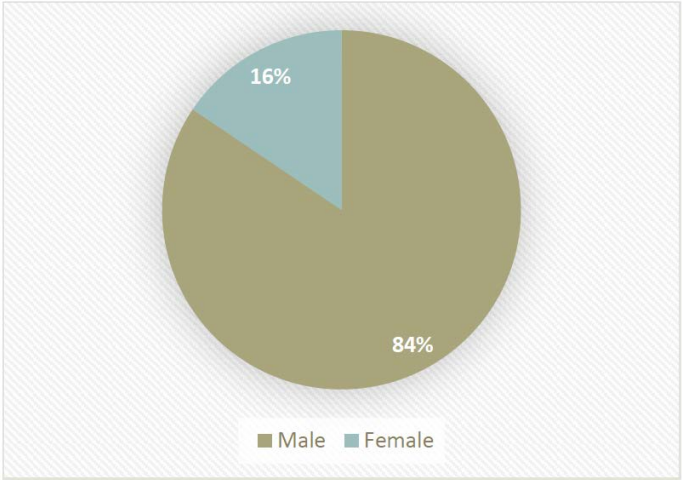

Figure 1: Gender Distribution of The Study Population

In all the 98 % cases, the intake was intentional while in 2% cases, the consumption of the poison occurred accidentally.

The following table describes the clinical evaluation of the patients.

Sr No	Characteristic	Observation
1	Mean Hospital Stay duration	5.5 ± 3.49 days
2	Requirement of mechanical ventilation (MV)	34 (34%)
3	Presence of shock	19 (19%)
4	Presence of metabolic acidosis	21 (21%)
5	Mean Total Atropine dose	133.2 ± 64.2 mg
6	Mean Plasma Cholinesterase level at admission	697.5 ± 187.5 IU/L
7	Serum Creatine kinase level at 48hours (mean)	338.12 ± 193 IU/L
8	Mortality	21(21%)

Table 2: Clinical and Laboratory Evaluation of the Patients

The study population had mean hospital stay duration of 5.5 ± 3.49 days. The overall mortality was 21%.34% patient's required mechanical ventilation at least once during the admission. Circulatory shock was present in 19% patients.21% patients had metabolic acidosis which required correction. the mean atropine dose given to the patients was 133.2 ± 64.2 mg.the mean plasma cholinesterase of the study population at admission was 697.5 ± 187.5 iu/l. the mean serum creatine kinase level of the study population at 48 hours after consumption was 338.12 ± 193 iu/l.

Analysis of outcome parameters and serum enzymes:

A. Creatine Kinase - The mean serum creatine kinase level of the study population at 48 hours after consumption was 338.12 ± 193 IU/L. The total number of patients who had raised CPK were 36 (36%). The outcome parameters based on raised and normal CPK levels are described below.

B. Table 3

parameter	normal Creatine Kinase (n=64)	raised creatine kinase (n=36)	value
hospital Stay	4.9 ± 2.1 days	6.4 ± 2.8 days	0.039
MV requirement	3 (28.1%)	16(44.4%)	0.044
P.Cholinesterase level	723.5 ± 243.6 IU/L	609.8 ± 159.1IU/L	0.062
Mean Total Atropine dose	103.5 ± 43.5 mg	186.3 ± 49.7mg	0.019
Mortality	11(17.2%)	10(27.8%)	0.039 HR: 1.6

The mean hospital stay for the patients of normal and raised creatine kinase group was 4.9 ± 2.1 days and 6.4 ± 2.8 days respectively. This difference was statistically significant with a p value of 0.039. The mechanical ventilation requirement was significantly higher (0.044) in the patients with raised creatine kinase (44.4%) than the patients with normal serum creatine kinase (28.1%).There were no statistically significant differences however numerically lower levels of plasma cholinesterase levels (p=0.062). The mean values were 609.8 ± 159.1 IU/L and 723.5 ± 243.6 IU/L respectively for the patients with raised and normal serum creatine kinase. The mean atropine dose required was significantly higher (p=0.019) in the patients with raised serum creatine kinase levels than those with normal levels. The mean atropine dose administered during the hospital stay was 103.5 ± 43.5 mg and 186.3 ± 49.7 in the normal and raised serum creatine kinase groups respectively. The mortality of the patients with raised serum creatine kinase was significantly higher (0.039) than the patients with normal levels. The mortality rate was 17.2% and 27.8% in the patients with normal and raised serum creatine kinase levels.

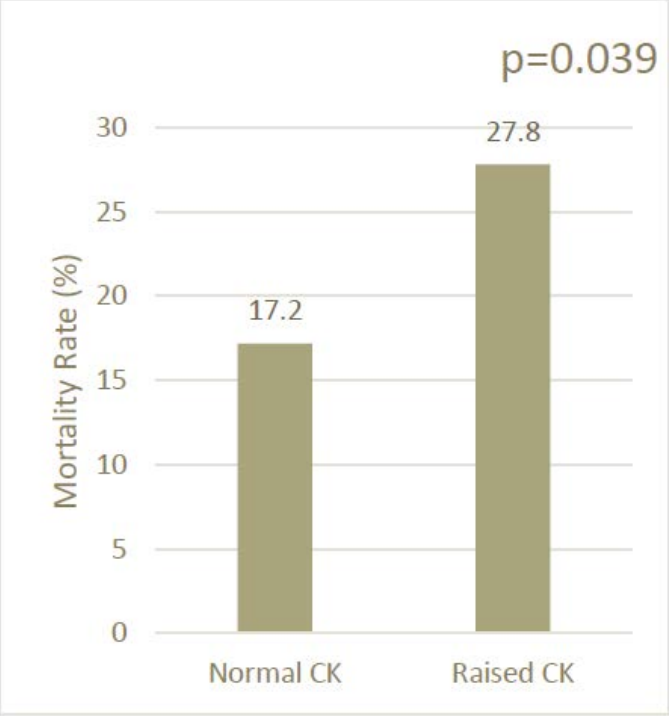

Figure 2: Mortality Rate and Serum Creatine Kinase Relationship

We performed a correlation analysis with the quantitative outcome variables and the serum enzyme values to calculate the Pearson's correlation coefficient. The results of this correlation are described below. As described in

the table below Serum creatine kinase demonstrated mild inverse correlation with plasma cholinesterase and moderate strength of correlation with hospital stay duration and total atropine dose. Person's correlation coefficient is interpreted (irrespective of positive/negative) in strength of correlations as

- ✓ >0.75: Strong
- ✓ 0.5 to 0.75: Moderate
- ✓ 0.25 to 0.5: Mild
- ✓ <0.25: = not significant

	Hospital Stay	Plasma Cholinesterase	Total Atropine dose
serum Creatine kinase	0.657 (Moderate)	-0.336 (Mild)	0.724 (moderate)

Table 4: Pearson's Correlation Coefficient for the Analysis

Discussion

OP compounds are the most commonly used pesticides in agriculture. Inhibition of acetylcholinesterase is the major mechanism of cholinergic crisis, which leads to stimulation of muscarinic and nicotinic receptors. Various clinical markers can be relevant in evaluation of the patients but the role of serum enzymes such as creatine kinase have been studied with many contradictory reports in the literature, which led us to plan this study to understand the levels of serum creatine kinase in the patients of OP poisoning and their correlation with the outcomes. We recruited a total of 100 cases of acute OP poisoning in this study which was conducted as an observational prospective design in which patients were followed up from admission to the discharge or death. We observed that the patients being admitted were of younger age group (mean age = 32.4 ± 13.5 years) with male predominance (M:F gender ratio of approximately 5:1). Our study is one of the higher sample size studies conducted in the patients of OP poisoning and thus may reflect a more relevant picture representative of the larger population. The works of Bhattacharya et al, Kumar et al, Raddi et al have described the clinical features and epidemiological data of OP poisoning in India and the clinical profile of our study population resembles their reports, probably because of the similar population geography [6, 8, 10]. The mortality rate described by Muley et al was 10.25%. The other studies by Kumar et al, Bhattacharyya et al, Raddi et al, Hassan et al have reported variable mortality rates which ranged from 7% to as high as 45% [8, 6, 11, 10]. The mortality rate depends upon the type and amount of the compound consumed and thus this has been associated with variabilities among the previous and current study with 27.8% mortality in our study.

The Outcome Parameters We Studied Included Average Hospital Stay, Mortality, Total Atropine Dose, Plasma Cholinesterase Levels And Requirement Of Mechanical Ventilation. It Has Been Shown That Plasma Cholinesterase Levels Correlate With The Treatment Prognosis And Severity Of Poisoning [12]. We Observed That The Patients Who Had Raised Creatine Kinase Levels Had Significantly Higher Mortality, Hospital Stay, Total Atropine Dose And Necessity For Mechanical Ventilation. The Relationship With Plasma Cholinesterase Was Not Statistically Significant. The Correlation Of Creatine Kinase With Total Atropine Dose And Hospital Stay Was Also Of Moderate Strength While The Same With Plasma Cholinesterase Was Of Mild Strength.

Raddi et al conducted an observational study to evaluate the prognostic significance of Creatine kinase in organophosphorus poisoning [10]. The mortality in this study in patient with elevated creatine kinase was 39.47%

as against 4.76% in patients with normal creatine kinase. These results almost completely echo the findings of our study and based on the current literature, we derive that with few exceptions, many studies have reported correlation of serum creatine kinase with outcomes in OP poisoning and our study adds importance evidence to these revelations with support of quantitative correlation we reported.

Our observations suggest that serum creatine kinase can be considered as one of the prognostic markers in the OP poisoning patients. . Our study however, could not be without limitations. We did not stratify the patients based on the specific type of OP compound. We also did not include a specific severity of the OP poisoning patients. We followed the patients only until their discharge form the hospital or the death. A correlation of enzymes over a subacute course could have been more useful towards predicting their role in recovery of the patients.

Conclusion

Serum creatine kinase can be used as significant prognostic indicator in patient of organophosphorus poisoning and helpful in predicting outcome.

References

1. Aring C. The systemic nervous affinity of triorthocresyl phosphate (jamaica ginger palsy). Brain. 1942; 65:34–47.
2. Jeyaratnam J. Acute pesticide poisoning: A major global health problem. World Health Stat Q. 1990; 43:139–44.
3. Pore NE, Pujari KN, Jadkar SP. Organophosphorus poisoning. J Pharma Biosci. 2011;2:604–12.
4. Bong SM, Moon JH, Nam KH, Lee KS, Chi YM, Hwang KY. Structural studies of human brain‐type creatine kinase complexed with the ADP–Mg2+–NO3−–creatine transition‐state analogue complex. FEBS letters. 2008 Nov 26;582(28):3959-65.
5. Wallimann T, Wyss M, Brdiczka D, Nicolay K, Eppenberger HM. Intracellular compartmentation, structure and function of creatine kinase isoenzymes in tissues with high and fluctuating energy demands: the'phosphocreatine circuit'for cellular energy., Biochemical Journal. 1992 Jan 1;281(Pt 1):21.
6. Bhattacharya K, Phaujdar S, Sarkar R, Mullick OS. Serum creatine phosphokinase: A probable marker of severity in organophosphorus poisoning. Toxicol Int. 2011;18:117–23.
7. Senanayake N, Karalliedde L. Neurotoxic effects of organophosphorus insecticides. An intermediate syndrome. N Engl J Med. 1987; 316:761–3.
8. Kumar GC, Bhuvana K, Venkatarathnamma PN, Sarala N. Serum creatine phosphokinase as predictor of intermediate syndrome in organophosphorus poisoning. Indian journal of critical care medicine., 2015 Jul;19(7):384.
9. Rosalki SB. An improved procedure for serum creatine phosphokinase determination. J Lab Clin Med. 1967;69:696–05.
10. RaddiD, Anikethana GV. Creatine Kinase for Prognostication in Organophosphorus Poisoning. International Journal of Science and Research.2012;5:2319-2323.
11. Hassan NA, Madboly AG. Correlation between Serum Creatine Phosphokinase and Severity of Acute Organophosphorus Poisoning: A Prospective Clinical Study (2012-2013). IOSR Journal of Environmental Science, Toxicology And Food Technology (IOSR-JESTFT)., 2013;4:18-29.
12. Chougule A, Hussain S, Agarwal DP. Prognostic and diagnostic value of serum pseudocholinesterase,

serum aspartate transaminase, and serum alinine transaminase in malignancies treated by radiotherapy. Journal of cancer research and therapeutics., 2008 Jan 1;4(1):21.