International Journal of Advances in Medicine
Nimsarkar AD et al. Int J Adv Med. 2023 Feb;10(2):125-130
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: https://dx.doi.org/10.18203/2349-3933.ijam20230059

Original Research Article

Serum creatine phosphokinase as a marker of severity and prognosis in organophosphorus compound poisoning

Ashish D. Nimsarkar*, Chandrashekhar M. Atkar

Department of Medicine, Government Medical College and Hospital, Nagpur, Maharashtra, India

Received: 30 November 2022
Revised: 03 January 2023
Accepted: 07 January 2023

***Correspondence:**
Dr. Ashish D. Nimsarkar,
E-mail: drashishnimsarkar@rediffmail.com

ABSTRACT

Background: Various newer biomarkers for organophosphorus (OP) compound poisoning are being looked at from diagnostic and prognostic perspectives. The present study was conducted to observe if serum creatine phosphokinase (CPK) can be used as a marker to assess the severity and monitor prognosis in patients of OP compound poisoning.
Methods: In this hospital based prospective, observational study, 100 duly screened patients presenting with OP compound were classified as per severity grade according to POP scale. Serum cholinesterase and serum CPK levels were assessed twice, on day 1 and on day 4; apart from requirements as per standard management protocol; and the levels were compared across severity grades of OP compound poisoning. Outcomes such as intermediate syndrome and need of intubation and chances of mortality were studied for correlation.
Results: There was statistically significant positive correlation between serum CPK level on day 1 as well as on day 4 with the severity of poisoning. The day 1 mean serum cholinesterase level also increased with the increase in severity of poisoning, but not the day 4 level. Significantly positive correlation was observed between serum CPK levels and development of intermediate syndrome, need of intubation and chances of mortality amongst cases.
Conclusions: Serum CPK can be used as an efficient marker of severity in the patients of OP compound poisoning and will be useful to predict prognosis and outcome.

Keywords: OP poisoning, Creatine phosphokinase, Cholinesterase, Severity, Prognosis

INTRODUCTION

Insecticidal/pesticidal poisoning is a major public health concern worldwide. The World Health Organization (WHO) estimates that globally nearly three million intentional or unintentional pesticide poisoning episodes occur annually and out of these, a minimum of 300,000 die.[1] Organophosphorus (OP) insecticides are one of the most common causes of morbidity and mortality due to poisoning worldwide, more so in India.[2,3] In an agricultural country like ours, where insecticidal compounds are easily available and widely used, it is only natural to witness OP poisoning cases relatively more than other countries. One estimate puts the number of OP poisoning encounters at around 1.27 lakh in the year 2007 in India.[4]

The quest for newer biomarkers in relation to OP compound poisoning started quite a long time back. OP labelled albumin in plasma, blood beta glucuronidase and paraxonase status have been suggested by some researchers to be very reliable marker for both diagnosis and prognosis.[5-9] But all these assays are dependent on access to specialised laboratories and are costly. The serum cholinesterase levels, their diagnostic and prognostic value and their relationship with the neurological syndromes (intermediate syndrome and delayed polyneuropathy) have been studied extensively. Most of the studies have shown that though serum cholinesterase can be used as a diagnostic marker, its role is minimal as a prognostic marker.[10,11] So cost-effective

and valid biomarker which could be utilised to predict the prognosis remains much desired.

Rhabdomyonecrosis has been observed to occur in animals after experimental OP poisoning, apart from evidence of muscle fibre necrosis in humans after OP compound poisoning.[12,13] Various parameters like serum creatine phosphokinase (CPK), serum lactate dehydrogenase (LDH), serum amylase, liver enzymes and urine creatinine levels are now being looked at as new biomarkers and their correlation with severity and prognosis of OP compound poisoning being studied. The present study was conducted to observe if serum CPK can be used as a marker to assess the severity and monitor prognosis in patients of OP compound poisoning.

METHODS

This was a hospital based prospective, observational study conducted over the period of 2 years (November 2016 – October 2018). The study was conducted in the department of Medicine, Government Medical College and Hospital, Nagpur (a tertiary care government teaching hospital in Central India).

The study population consisted of patients presenting with OP compound poisoning to the emergency department of the study centre. Sample size was estimated on the basis of following assumptions considering proportion of OP compound poisoning patients admitted: anticipated correlation coefficient between Peradeniya OP poisoning (POP) score and CPK level, r=0.352; power (1-β) %=90; α-error (%)=5; and estimated sample size=74.

Hence a sample size of 100 was considered adequate for our study.

Following selection criteria were adopted for the study:

Inclusion criteria

Patients presenting with history of organophosphate compound poisoning who arrived at the hospital within 6 hours of consumption, above the age of 12 years, after prior consent from the patient or their relatives.

Exclusion criteria

Patients with other co-existing illness (myopathy, chronic renal disease, epilepsy, myocardial infarction, myocarditis, autoimmune diseases, malignancy), patients who had trauma or received intramuscular injections and cardiopulmonary resuscitation recently, patients who are on prior medications like statins, fibrates, aspirin, anticoagulants, frusemide or dexamethasone, chronic alcoholics, patients presenting with consumption of alcohol along with poison and patients or relatives not giving consent for the study.

Approval from Institutional Ethics Committee was obtained before start of data collection of the study.

Study protocol

Patients were admitted in tertiary care centre with history of OP compound poisoning with written and informed consent from patients themselves or direct relatives were the study group.

The diagnosis of OP compound poisoning was based on the following criteria: history of exposure to or contact with OP compound, characteristic clinical signs and symptoms of OP compound poisoning and decreased serum cholinesterase activity.

Admissions were always through the emergency department where initial decontamination procedures were carried out. These included skin decontamination by removal of all clothing, washing skin and hair with soap and water and gastrointestinal decontamination by gastric lavage, cathartics and activated charcoal. They were then shifted to ICU for further management. All cases were treated with repeated doses of intravenous atropine and oximes as per standard protocols. Intubation and mechanical ventilation were done according to clinical need. A detailed clinical examination was done and information was collected through a preformed and pre-tested proforma from each patient. The following parameters were analysed for association of OP compound exposure- demography, age, sex, time of admission, interval between consumption and admission, reason for consumption, poison particulars, severity grade according to POP scale, symptoms after consumption, clinical presentation, pupil size, pulse rate, blood pressure, respiratory rate, secretions. The diagnosed patients were investigated. Complete blood counts, renal function test, liver function test, serum electrolytes, serum cholinesterase and serum creatine phosphokinase were acquired. Samples for serum cholinesterase and serum creatine phosphokinase were collected twice; on day 1 and on day 4. The value of serum cholinesterase 4900 IU – 11900 IU/l in males and 3930 IU – 10800 IU/l in females were taken as normal. The value of serum creatine phosphokinase 25 IU – 200 IU/l in males and 25 IU – 170 IU/l in females were considered normal.

Statistical analysis

Serum CPK level and serum cholinesterase level were compared between day 1 and day 4 by performing paired t-test. Serum CPK level and serum cholinesterase level were compared between day 1 and day 4 across severity of OP compound poisoning as per POP score by performing Wilcoxon sign rank test. Spearman correlation coefficient (rho) was calculated to assess correlation between severity of OP compound poisoning as per POP score with day 1 CPK level and dose of atropine used. Association of severity as per POP score with total atropine used and hospital stay was performed by calculating one-way non-

parametric analysis of variance (ANOVA) test. Categorical variables were compared between survivors and non-survivors by performing Chi-square test. For small numbers, Fisher exact test was used wherever applicable. P<0.05 was considered as statistical significance. Statistical package for the social sciences (SPSS) (version 16) was used for data analysis.

RESULTS

A total of 100 participants were studied and considered for final analysis after applying the inclusion and exclusion criteria amongst the study population. Seventy four percent of the study participants were males and 26% were females. Most of the patients were from the age group of 21-30 years (31%), followed by 31-40 years (27%) (Table 1).

Table 1: Demographic details of the participants.

Age in years	No. of cases	Male	Female
11–20	18	9	9
21–30	31	23	8
30–40	27	22	5
41–50	14	12	2
>50	10	8	2
Total	100	74	26
Mean age±SD (range)		28.19±12.12 (15-65)	35.35±11.91 (15-55)

Out of total 100 patients, 64% patients belonged to the low socio-economic class; 29% patients were from middle class; 4% patients belonged to lower middle class and 3% belonged to upper middle class. No patients were from upper socio-economic status. They were mostly farmers by occupation; others were housewives, students and labourers.

Around 92% of the participants had consumed poison with the intention of suicide and rest of the patients had accidental exposure. 41% of patients had consumed chlorpyrifos, while monocrotophos was the second commonest (16%). Other compounds majorly used were profenofos (14%), dichlorovos (11%) and quinolphos (6%). Vomiting (89%) was the commonest symptom, while the commonest sign at presentation was fasciculation (86%). Miosis was present in 67% of patients and 56% patients had altered sensorium at the time of admission. Other presenting features were frothing (36%), bradycardia (13%) and convulsions (9%).

Out of total 100 patients, 74 recovered without developing intermediate syndrome. 19 patients (19%) developed intermediate syndrome; of which 12 patients recovered while 7 patients died. Remaining 7 patients died without developing intermediate syndrome. Thus, 86 patients (86%) recovered while 14 patients died (14%) during the study. The mean time to reach the hospital was 3.42±1.08 hours. The correlation of mean time interval required to reach hospital with clinical outcome was found to be statistically significant with p<0.001. The break-up of time interval by hours and its correlation with clinical outcome is detailed in Table 2.

According to POP score, 46%, 47% and 7% patients were grouped into mild, moderate and severe cases of poisoning respectively. The difference between day 1 and day 4 mean serum CPK levels was found to be statistically significant during comparison across severity grades as per POP scale (p<0.05). Similarly, mean serum cholinesterase levels also varied significantly between day 1 and day 4 across grades of severity as per POP scale (p<0.05) (Table 3).

The mean serum CPK level on day 1 in patients who developed intermediate syndrome was 1146.15±548.86 IU/l. The mean serum CPK level on day 1 in patients who did not develop intermediate syndrome was 382.26±409.86 IU/l. The correlation was found to be statistically highly significant (p<0.001). In the 19 patients who developed intermediate syndrome, the mean serum cholinesterase level on day 1 was 846.89±276.42 IU/l while it was 1300.50±1149.06 IU/l in those who did not develop intermediate syndrome. The relation was not found to be statistically significant (p=0.0656) (Table 4).

Forty percent patients were intubated while 60% patients were on spontaneous breathing and were managed without intubation. The mean day 1 serum CPK level in the patients who were intubated was 927.76±500.68 IU/l, while it was 260.49±353.66 IU/l in the patients who were not intubated. The correlation between day 1 CPK level and need of intubation was found to be statistically highly significant (p<0.001). The mean day 1 serum cholinesterase level in the patients who were intubated was 1169.87±1324.52 IU/l while the mean day 1 serum cholinesterase level in the patients who were not intubated was 1243.95±839.89 IU/l. The correlation between day 1 serum cholinesterase level and need of intubation was found to be statistically insignificant (p>0.05) (Table 3).

As for the dose of atropine required for management, the patients who had mild poisoning required 65.60±20.60 mg. The patients who had moderate poisoning required 161.19±29.05 mg. The patients who had severe poisoning required 329.14±15.95 mg of atropine. The difference was found to be statistically highly significant (p<0.001). The mean hospital stay of patients with mild, moderate and severe poisoning were 6.21±1.51 days, 9.76±2.59 days and 8.85±3.57 days (p<0.001).

The difference between day 1 and day 4 mean serum CPK levels was observed to be statistically significant across various clinical outcome categories, the result being highly significant among those recovered (Table 5).

As for the need of intubation and mortality and their correlation with severity of poisoning and day 1 serum CPK level; in the patients with mild poisoning (n=46), the

mean serum CPK level was 231.65±391.17 IU/l. Out of total patients, 4 patients (8.7%) were intubated and 1 patient (2.2%) died. In the patients with moderate poisoning (n=47), the mean serum CPK level was 685.62±465.51 IU/l. Of these patients, 29 patients (61.7%) were intubated and 6 among them (12.8%) died. In the patients with severe poisoning (n=7), the mean serum CPK level was 1408.60±242.19 IU/l. All 7 of them (100%) were intubated and all of them (100%) died (Table 6).

Table 2: Correlation of mean time interval required to reach hospital with clinical outcome.

Time (hours)	No. of cases	Clinical outcome (%)				P value
		Deaths	IMSD	IMSR	Recovery	
1–2	20	2 (10)	2 (10)	1 (5)	15 (75)	<0.001
3–4	62	2 (3.2)	5 (8.1)	5 (8.1)	50 (80.6)	
5–6	18	3 (16.7)	0	6 (33.3)	9 (50)	
Total	100	7 (7)	7 (7)	12 (12)	74 (74)	

IMSD- Intermediate syndrome death, IMSR- intermediate syndrome recovery

Table 3: Comparison of day 1 and day 4 mean serum CPK levels and mean serum cholinesterase levels across severity grades as per POP score.

Severity as per POP scale	CPK level		P value	Cholinesterase level		P value
	Day 1	Day 4		Day 1	Day 4	
Mild	231.65±391.17	288.76±247.70	0.0023	1418.23±1362.05	3525.37±954.86	<0.0001
Moderate	685.62±465.51	1192.09±739.16	<0.0001	1070.78±692.95	2847.59±962.09	<0.0001
Severe	1408.6±242.19	2437.64±627.92	0.0180	838±347.51	2696.57±613.68	0.018

Table 4: Correlation of day 1 serum CPK level, day 1 serum Cholinesterase level with intermediate syndrome and need of intubation.

Clinical parameter	No. of cases	Mean day 1 CPK level (IU/l)	Mean day 1 cholinesterase level (IU/l)
Intermediate syndrome			
Yes	19	1146.15±548.86	846.89±276.42
No	81	382.26±409.86	1300.50±1149.06
P value		<0.0001	0.0656
Requirement of intubation			
Yes	40	927.76±500.68	1169.87±1324.52
No	60	260.49±353.66	1243.95±839.89
P value		<0.0001	0.2104

Table 5: Comparison of mean serum CPK level and clinical outcome.

Clinical outcome	Serum CPK level (IU/l)		P value
	Day 1	Day 4	
Death	1101±272.37	1890.5±390.62	0.0180
IMSD	1309.14±628.91	2065.82±1072.91	0.0180
IMSR	1051.07±500.44	1664.60±1023.18	0.0186
Recovery	314.27±351.82	523.04±449.57	<0.0001

Table 6: Correlation of severity of poisoning, day 1 serum CPK level with need of intubation and mortality.

Severity of poisoning	No. of cases	Day 1 serum CPK level	Number of patients intubated (%)	Mortality (%)
Mild	46	231.65±391.17	4 (8.7)	1 (2.2)
Moderate	47	685.62±465.51	29 (61.7)	6 (12.8)
Severe	7	1408.60±242.19	7 (100)	7 (100)
P value		0.0001	<0.001	<0.001

DISCUSSION

The present study was conducted to observe if serum CPK can be used as a marker to assess the severity and monitor prognosis in patients of OP compound poisoning. Data of a total of 100 participants were studied and analysed.

Suicidal mode of OP poisoning being observed to be responsible in overwhelming majority of the cases (92%) is not surprising, given the rampant usage, the free availability of and ease of access to the compounds in India, much higher than the incidence in western countries.[14,15] Male gender predilection (74% of the patients) and the affection of age group of 21-40 years (58%) are in line with the observations of Mural et al, Chetan et al and Sen et al.[16-18] This young, male preponderance is probably due to the fact that they are emotionally more stressed out due to joblessness, which make them more vulnerable to take drastic steps like suicide. Most of the patients belonged to lower (64%) and middle (29%) socio economic status as per modified Kuppuswamy scale, which was in consensus with Bhattacharya et al, amongst other studies.[19] Chlorpyrifos (41%) was the most commonly used compound followed by monocrotophos (16%), profenophos (14%), dichlorovos (11%) and quinolphos (6%); the distribution being similar to that previously observed.[16-19] Majority of patients in our study had experienced at least one episode of vomiting, similar to the study of Bhattacharya et al (87.3%).[19] The high incidence of fasciculation (86%) is not in sync with the previous observations though, for reasons unknown.

The POP score has been shown to predict the severity, morbidity and mortality of OP poisoned patients.[20] In our study, the proportion of mild, moderate and severe poisoning as per POP score were 46%, 47% and 7% respectively. It was 83%, 11% and 6% respectively in the study done by Mural et al; while the proportion was 27%, 50.8% and 22.2% in Bhattacharya et al study.[16,19]

The mean serum cholinesterase levels on day 1 were 1418.23, 1070.78 and 838.00 (IU/l) in mild, moderate and severe cases in the present study. In the Mural R et al study, the mean serum cholinesterase were 2389, 1104.4 and 237.5 (IU/l) in mild, moderate and severe group respectively; while they were at 5838.8, 2077.2, 607.4 (IU/l) in the study conducted by Hassan et al.[14,16] Bhattacharya et al 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 poisoning cases.[19] Thus, on the basis of observations from present study and review of previous studies, it is evident that as the severity of poisoning goes on increasing, the value of serum cholinesterase goes on decreasing.

In the present study, the serum CPK level were measured serially on day 1 and day 4. The mean serum CPK levels on day 1 were 231.65, 685.62 and 1408.60 (IU/l) in mild, moderate and severe cases respectively. In the study conducted by Mural R et al, the mean serum CPK levels on day 1 were 183.10, 489.90 and 2139.80 (IU/l) in mild, moderate and severe poisoning.[16] In the study conducted by Bhattacharya et al, the respective mean serum CPK levels were observed to be 273.53, 456.06 and 1032.57 (IU/l); while they were reported at 89.1, 273.0 and 688.8 (IU/l) in the study done by Hassan et al.[14,19] Sen et al calculated the mean serum CPK level in the survivors and non survivors and found them to be at 698.58 and 1277.81 (IU/l) respectively.[18] On day 4, the mean serum CPK level in the present study were 288.76, 1192.09 and 2437.64 (IU/l) in mild, moderate and severe poisoning respectively. Mural et al measured the serum CPK level on day 3; the levels were 588.1, 1873.3 and 3263.0 in mild, moderate and severe poisoning respectively.[16] In the study conducted by Bhattacharya et al, the final serum CPK level were 205.88, 610.97 and 3373.67 (IU/l).[19] Sen et al measured the values of mean serum CPK level in the survivor and non-survivor groups serially and the values on day 4 were 595.37 and 1180.54 (IU/l) respectively.[18] Statistically significant positive correlation of initial serum CPK levels with POP score and negative correlation of initial serum CPK with serum cholinesterase levels was noted.

Thus, the present study delineates a high degree of correlation between the severity of OP poisoning and the initial serum CPK levels. The serum CPK levels were reported markedly raised in patients with intermediate syndrome on day 1 as well as on day 4. Also, a high degree of correlation was noted between initial serum CPK levels and need for intubation and mechanical ventilation as well as chances of mortality, further reinforcing the hypothesis.

Few limitations of the present study are worth mentioning. The sample size was relatively small. This was a single centre study, and hence the external validity will have to be guarded.

Lastly, the findings are to be seen in light of non-specificity of elevated CPK, though other conditions potentially increasing the CPK levels were excluded during patient selection to the extent possible.

CONCLUSION

The serum CPK can be used as an efficient marker of severity in the patients of OP compound poisoning. The serum cholinesterase serves as a diagnostic parameter in OP compound poisoning but it cannot predict the prognosis and outcome of the patients; while serum CPK can be used to predict the prognosis and outcome of the patients as well. Further multi-centre studies with larger sample size are recommended for substantiation.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Jeyaratnam J. Acute pesticide poisoning: a major global health problem. World Health Statistics Quarterly. 1990;43(3):139-44.
2. Batra AK, Keoliya AN, Jadhav GU. Poisoning: an unnatural cause of morbidity and mortality in rural India. J Assoc Physicians India. 2003;51:955-9.
3. Chatterjee S, Riaz H. Death by insecticide. BMJ. 2013;346.
4. Ravi G, Rajendiran C, Thirumalaikolundusubramanian P, Babu N. Poison control, training and research center, Institute of Internal Medicine, Government General Hospital, Madras Medical College, Chennai, India. In 6th Annual congress of Asia Pacific Association of Medical Toxicology, Bangkok, Thailand. 2007;2-14.
5. Agarwal SB, Bhatnagar VK, Agarwal A, Agarwal U, Venkaiah K, Nigam SK, Kashyap SK. Impairment in clinical indices in acute organophosphate insecticide poisoning patients in India. Int J Toxicol. 2007;4(1).
6. Peeples ES, Schopfer LM, Duysen EG, Spaulding R, Voelker T, Thompson CM, Lockridge O. Albumin, a new biomarker of organophosphorus toxicant exposure, identified by mass spectrometry. Toxicol Sci. 2005;83(2):303-12.
7. Li B, Ricordel I, Schopfer LM, Baud F, Mégarbane B, Nachon F, Masson P, Lockridge O. Detection of adduct on tyrosine 411 of albumin in humans poisoned by dichlorvos. Toxicol Sci. 2010;116(1):23-31.
8. Soltaninejad K, Shadnia S, Afkhami-Taghipour M, Saljooghi R, Mohammadirad A, Abdollahi M. Blood β-glucuronidase as a suitable biomarker at acute exposure of severe organophosphorus poisoning in human. Human Exp Toxicol. 2007;26(12):963-6.
9. Costa LG, Cole TB, Vitalone A, Furlong CE. Measurement of paraoxonase (PON1) status as a potential biomarker of susceptibility to organophosphate toxicity. Clinica Chimica Acta. 2005;352(1-2):37-47.
10. Yun HW, Lee DH, Lee JH, Cheon YJ, Choi YH. Serial serum cholinesterase activities as a prognostic factor in organophosphate poisoned patients. Hong Kong J Emerg Med. 2012;19(2):92-7.
11. Aygun D, Doganay Z, Altintop L, Guven H, Onar M, Deniz T, Sunter T. Serum acetylcholinesterase and prognosis of acute organophosphate poisoning. J Toxicol Clin Toxicol. 2002;40(7):903-10.
12. Vanneste Y, Lison D. Biochemical changes associated with muscle fibre necrosis after experimental organophosphate poisoning. Human Exp Toxicol. 1993;12(5):365-70.
13. John M, Oommen A, Zachariah A. Muscle injury in organophosphorous poisoning and its role in the development of intermediate syndrome. Neurotoxicology. 2003;24(1):43-53.
14. Hassan NA, Madboly AG. Correlation between serum creatine phosphokinase and severity of acute organophosphorus poisoning: A prospective clinical study (2012-2013). IOSR J Env Sci Toxicol Food Technol. 2013;4:18-29.
15. Weissman-Brenner A, David A, Vidan A, Hourvitz A. Organophosphate poisoning: a multihospital survey. IMAJ-RAMAT GAN. 2002;4(7):573-6.
16. Mural R, Bajaj G, Mammen D. Study of level of total serum creatine phosphokinase as prognostic indicator in acute organophosphorus poisoning: a prospective study. Int J Contemp Med Res. 2017;4(2):578-82.
17. Kumar GC, Bhuvana K, Venkatarathnamma PN, Sarala N. Serum creatine phosphokinase as predictor of intermediate syndrome in organophosphorus poisoning. Indian J Crit Care Med. 2015;19(7):384.
18. Sen R, Nayak J, Khadanga S. Study of serum cholinesterase, CPK and LDH as prognostic biomarkers in Organophosphorus Poisoning. Int J Med Res Rev. 2014;2(3):185-9.
19. Bhattacharyya K, Phaujdar S, Sarkar R, Mullick OS. Serum creatine phosphokinase: A probable marker of severity in organophosphorus poisoning. Toxicol Int. 2011;18(2):117.

Cite this article as: Nimsarkar AD, Atkar CM. Serum creatine phosphokinase as a marker of severity and prognosis in organophosphorus compound poisoning. Int J Adv Med 2023;10:125-30.