

The utility of serial serum cholinesterase as a prognostic marker in organophosphorus compound poisoning

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ABSTRACT

Background: Acute organophosphorus (OP) poisoning is one of the most common poisonings in India contributing to significant morbidity and mortality. Irreversible inhibition of cholinesterase enzymes is attributed to the serious clinical outcomes in these patients, which is assessed by the estimation of serum cholinesterase (SChE) levels. The present study was undertaken to evaluate the utility of serial estimation of SChE levels in patients of OP poisoning in predicting the clinical outcome.

Methods: Medical records of 31 patients from January 2013 to December 2013 admitted in our institute with acute OP poisoning were analyzed for SChE at admission, 48 hrs, 72 hrs and 120 hrs after admission. Data regarding clinical findings at admission and outcomes were recorded.

Results: Monocrotophos (55%) was the most commonly used OP compound. Mean serial SChE levels (in KU/L) at admission, 48, 72, and 120 hrs in patients who survived are 0.18 ± 0.10 , 0.28 ± 0.14 , 0.41 ± 0.21 , 0.46 ± 0.16 and in patients who expired are 0.02 ± 0.01 , 0.05 ± 0.02 , 0.03 ± 0.02 , 0.03 ± 0.02 , respectively. SChE levels at admission in survived group, compared to those in expired group were statistically significant ($p < 0.001$). About 92% patients in moderate to severe grade of poisoning (SChE levels < 0.2 KU/L) were mechanically ventilated. The relationship between serial SChE levels in survival group and was found to be statistically significant ($p < 0.01$).

Conclusion: In the present study, significant increase in serial SChE levels were correlating with better clinical outcome as evidenced by an improvement with mechanical ventilation and survival rates in acute OP poisoning.

Keywords: Organophosphorus poisoning, Serial serum cholinesterase levels, Mechanical ventilation, Prognostic marker

INTRODUCTION

Poisoning is a one of the common methods of self-harm, especially in the developing world.¹ According to World Health Organization report, 3 million cases of pesticide poisoning occur annually globally, and most of them are in Asia of which at least half of them are due to organophosphorus (OP) poisoning.² India being an agricultural country, OP compounds due to their easy availability are among the most commonly used agents for suicidal poisoning.³ Most of the self-poisoning deaths in South and Central India are due to OP compounds.⁴⁻⁶ Among the different compounds used, majority of deaths were due to poisoning with monocrotophos and endosulfan.⁷ In different Indian studies mortality rates range from 10.3% to 43.8%.^{8,9} OP pesticides act by inhibiting acetyl cholinesterase (AChE) and serum cholinesterase (SChE) resulting in accumulation

of acetylcholine at synapses and myoneural junction leading to cholinergic over activity in the peripheral and central nervous system. At high doses, there is depression of the respiratory center in the brain, followed by peripheral neuromuscular blockade causing in respiratory paralysis and death.^{10,11} SChE levels have been used for estimating the degree of inhibition of the enzyme to assess the severity of poisoning according to Proudfoot criteria.¹² Serial estimation of SChE levels can detect the persistent enzyme inhibition. In most of the poisoning cases, the type of OP poison and the quantity consumed by the patient are unknown necessitating the need of serial estimation of serum AChE. There are few studies estimating the serial SChE in first few days of poisoning where the likelihood of developing life-threatening complications is considerable. SChE levels will be an effective laboratory diagnostic aid to guide the course of early management of serious OP poisoning cases with

respect to their outcome assessed by the need of mechanical ventilation and mortality.

This observational study was done to evaluate the prognostic value of measuring serial SChE levels in patients with OP poisoning for predicting the clinical outcome.

METHODS

The present study was done in the Department of Clinical Pharmacology and Therapeutics at Nizam's Institute of Medical Sciences. The study was approved by Institutional Ethics Committee. Medical records of OP poisoning cases admitted during January 2013 to December 2013 were retrieved from medical records department. The detailed demographic, clinical data along with serial SChE levels at admission and 48, 72, and 120 hrs were recorded in the case record forms. SChE levels were determined by measuring the rate of hydrolysis of substrate (benzyl choline) catalyzed by SChE using ultraviolet-visible spectrophotometer. The procedure included the addition of 20 μ l of patient's serum with 2 ml of phosphate buffer solution, 1 ml of substrate (Benzyl choline) and 1 ml distilled water. The mixture was mixed, and the absorbance at 240 nm at 30 secs interval was observed for 2 mins. The difference in absorbance was considered for SChE activity. The normal SChE range from above method ranges from 0.6 to 1.4 KU/L. The patients were divided into mild (<10% reduction of SChE i.e. 0.2-0.6 KU/L), moderate (10-50% reduction of SChE i.e. 0.1-0.2 KU/L) and severe (>50% reduction of SChE i.e. <0.1 KU/L) grades of poisoning based on Proudfoot criteria. Patients with history of poisoning with double insecticide, multiple poisoning with other drugs such as opioids, diazepam, barbiturate, etc., malnutrition and patients with chronic hepatic illness were excluded.

Statistical analysis

Statistical analysis was performed using the tabulated data from the case record forms of patients with OP poisoning. Data were presented either as mean \pm standard deviation (SD) or as a percentage. The serial SChE levels at various time points were analyzed by ANOVA. Paired and unpaired 't' test are used compare significance between the groups at serial time points. Fisher's exact test was performed to analyze categorical data. The level of significance was set at $p < 0.05$ with a power of 80%. All statistical analysis was performed using the Graph Pad prism software (version 4, USA).

RESULTS

Medical records of 52 patients of either – gender with definitive history of OP poisoning admitted between January 2013 and December 2013 were reviewed and excluded 21 patients meeting the exclusion criteria. A total of 31 patients were included in the study. The mean age

of patients was 28.25 ± 7.26 years. Poisoning cases were more common in males (71%) and the majority of them are from rural areas (75%) with agriculture as occupation in approximately half of the cases. The OP compounds used for self-poisoning were monocrotophos which accounted for 55%, chlorpyrifos 25%, methyl parathion 10% and unknown OP compounds (10%).

The serial SChE levels (KU/L) estimated at admission, 48, 72, and 120 hrs for the group of patients who survived (0.18 ± 0.10 , 0.28 ± 0.14 , 0.41 ± 0.21 , and 0.46 ± 0.16 , respectively) and those who expired (0.02 ± 0.01 , 0.05 ± 0.02 , 0.03 ± 0.02 , and 0.03 ± 0.02 , respectively) are shown in Figure 1. The SChE levels are compared among survivors versus expired groups. A significant improvement in the serial SChE levels were observed in 25 patients from survived group, compared to 6 patients in expired group. Further mean SChE levels recorded at the time of admission in patients of survived group (0.18 ± 0.10) were significantly higher than those in the expired group (0.02 ± 0.01).

In the present study, the number of patients on mechanical ventilation and number of patients with their clinical outcome assessed as either expired or survived in mild, moderate and severe degree of poisoning and their correlation with SChE were analyzed. A total of 2 patients of the 7 in mild degree poisoning, 11 patients out of 13 in a moderate degree and all 11 patients in severe degree of poisoning were requiring mechanical ventilation at admission as shown in Table 1.

It was observed that there was no mortality in mild degree poisoning ($n=7$), whereas mortality was observed in 1 patient of moderate degree ($n=13$) and 5 patients in severe degree poisoning ($n=11$) as shown in Table 2.

The serial activities of the SChE level were recorded to analyze the trend of enzyme activity in all patients at successive time points (time of admission, 48, 72, and 120 hrs). The progressive increase in the serial SChE levels were seen to be correlating with the group of patients who

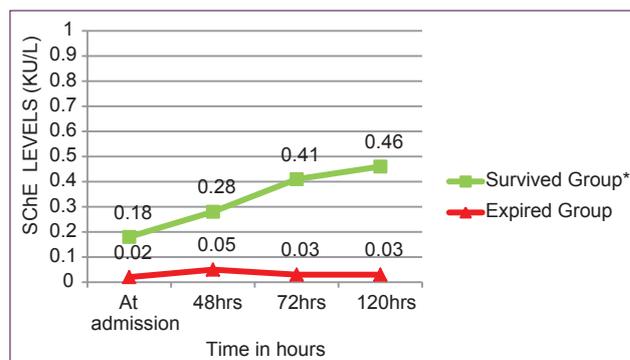


Figure 1: Mean serial serum cholinesterase (SChE) levels in survived and expired groups.

*** $p < 0.001$, Serial increase in SChE levels at admission, 48, 72, and 120 hrs. # $p < 0.001$, SChE levels 'at admission' between survived and expired groups.**

Table 1: Mechanical ventilation and its relation to different grades of OP poisoning.

	Mild (0.2-0.6 KU/L) %	Moderate (0.1-0.2 KU/L) %	Severe (<0.1 KU/L) %	p value
Mechanical ventilation	28.57	84.6	100	<0.001
Not on mechanical ventilation	71.43	15.4	Nil	

p<0.001 (between those on mechanical ventilation and not on mechanical ventilation in mild, moderate and severe groups of OP poisoning). OP: Organophosphorus

Table 2: Clinical outcome (mortality/survival) and its relation to different grades of OP poisoning.

	Mild (0.2-0.6 KU/L) %	Moderate (0.1-0.2 KU/L) %	Severe (<0.1 KU/L) %	p value
Expired group	Nil	7.7	45.4	<0.05
Survived group	100	92.3	54.6	

p<0.05 (between survived group vs. expired group in mild, moderate and severe groups of OP poisoning). p<0.05 (between survived group vs. expired group in mild, moderate and severe groups of OP poisoning). OP: Organophosphorus

survived in total 31 patients, as calculated by fisher's exact test and found to be statistically significant (p<0.01) as shown in Table 3.

DISCUSSION

OP poisoning is an important medical emergency in developing nations like India where agriculture is an important profession for the majority of people, living in rural areas where access to highly toxic OP compounds is unrestricted. In most of the cases, there is lack of information on the type of poison consumed with suicidal intent, which is often compounded by limited tertiary care resources. These factors cause significant life-threatening complications and subsequently considerable mortality rate. OP compounds exert their toxic manifestations by irreversibly inhibiting the AChE, SChE and neuropathy target esterase leading to accumulation of acetylcholine at the synapse. Thus, hyperstimulation of the central and peripheral nervous systems has resulted in cholinergic crisis. The resulting muscarinic and nicotinic symptoms may continue for days or months until the cholinesterase enzyme gets reactivated. Estimation of OP exposure by cholinesterase levels helps healthcare professionals to establish early diagnosis and thereby institute immediate treatment plan.¹³ However, Eddleston et al. and Worek et al. believed that cholinesterase level estimation at a single time point lack sensitivity and specificity and thus might not be related to the severity of poisoning.^{14,15}

The present study was thus undertaken to evaluate the relationship between the serial estimation of SChE levels and the clinical outcome in OP poisoning patients. Incidence of OP poisoning was more predominant in younger age group (20-35 years), which is comparable to earlier studies done by Zavar.¹⁶ There was a male predominance with 71% of total patients in our study and with majority (65%) of patients with agricultural farming as a profession which is consistent with studies by Arup and Kavya et al.^{17,18} This association may possible because farming as a profession

Table 3: Survival and serial activity of SChE levels.

	Survived group (n=25) (%)	Expired group (n=6) (%)	p value
Serial SChE level elevated	20 (80)	1 (16.3)	<0.01
Serial SChE level not elevated	5 (20)	5 (83.7)	

p<0.01 (between survival and serial SChE level)

is largely taken up by males, in whom unrestricted access to life-threatening pesticides is seen in our country. In this study, monocrotophos was the most commonly used OP poison, followed by chlorpyrifos and methyl parathion, which is similar to study by Srinivas Rao Ch et al. done in a larger sample of the population.^{6,19}

In the present study, we observed significantly low level of SChE recorded at the time of admission. Serial SChE levels from time of admission until 120 hrs were significantly increased in patients who survived (p<0.001). A consistent increment in SChE levels with patients improving and a decrease in the SChE levels in those patients who are deteriorating were reported in previous studies by Kar and Routier et al.^{20,21} Similarly, studies done by Hassan et al. and Mehta et al. observed lower activity of SChE in more than 70% of cases at presentation in their studies.^{19,22,23} Aygun et al. found that SChE estimations are useful in diagnosis of OP poisoning in the acute phase, but show no relation to the severity of poisoning.²⁴ However, in our study, we observed a consistent relation between lower SChE levels and moderate to severe grade of poisoning given by Proudfoot criteria at the time of presentation.

We analyzed SChE levels at serial time points because a single measurement of SChE at admission may have no prognostic value, whereas serial SChE activity may predict patient's clinical outcome more accurately and assist in choosing better treatment options like the need for mechanical ventilation.

Further the levels were monitored at four successive time points from admission to 120 hrs because it is the time at which oximes ideally reach their peak activity and thereby decrease the need for mechanical ventilation in patients with severe respiratory distress.¹⁴ In this study, we observed a steady and significant improvement in SChE levels, in those patients showing better signs of improvement on mechanical ventilation as compared to that not on ventilation. Another study by Goswamy et al. concluded that apart from clinical indicators, low SChE levels have greatest predictive value for mechanical ventilation in OP poisoning.²⁵ However Noura et al. did not find any statistically significant difference in mean SChE levels in those mechanically ventilated and those not needing ventilatory support.²⁶

In a retrospective study by Srinivas Rao Ch et al. average mortality rate observed over 5 years was 22.6% as compared to 19.35 % in our study, which may probably be attributed to the tertiary health care facilities for mechanical ventilation and emergency care at our institute. According to a report by Chen et al. the absence of elevating SChE level within first 48 hrs of poisoning is associated with a higher mortality in acute OP poisoned patients.²⁷ The relationship between serial SChE activity with increasing trends had no mortality. Whereas there was a consistent association with persistently low levels of SChE and no significant rise of SChE activity in all the six expired patients. At our medical institute, SChE levels are serially measured if the patient does not improve, thus help in plan an individualized regimen with regard to ventilatory requirements and aggressively manage respiratory complications which form the most common cause of death. Medical management with cholinesterase reactivators and anticholinergics like atropine can also be individualized to treat effectively the cholinergic crisis, which often is associated with the poorer outcomes in patients with moderate to severe grades of OP poisonings.

CONCLUSION

In the present study, significant increase in serial SChE levels were correlating with better clinical outcome as measured by the improvement with mechanical ventilation and mortality rates in acute OP poisoning. However, further studies in the larger sample size will be needed to establish the importance of serial measurement of SChE as a prognostic marker.

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