

A study on serum cholinesterase levels as a prognostic marker in organophosphorus poisoning

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ABSTRACT

Background: Organophosphorus compound poisoning is the most common medico toxic emergency in India. Respiratory failure is the most common complication of OP poisoning leading to death. **Materials and methods:** Cross sectional study was done in Cases with history of exposure to organophosphorus compound within previous 24 hours was chosen after applying inclusion and exclusion criteria. Patients were evaluated for Peradeniya OP poisoning scale and serum cholinesterase levels for assessment of severity of poisoning. Serum cholinesterase levels and Peradeniya OP poisoning scale were studied to predict the complications and prognosis. **Results:** In our study ventilatory support required in 27.5% of patients. Mortality in our study was 17.5%. Only 15% of patients with mild grade of poisoning according to Peradeniya OP poisoning scale required ventilatory support, where as 85% did not require ventilatory support. Most of patients with moderate (45%) and severe poisoning (57%) according to Peradeniya OP poisoning scale required ventilatory support. 91% of patients with serum cholinesterase levels more than 50% did not require ventilatory support. Only 34% of patients with serum cholinesterase levels less than 50% required ventilatory support. In our study there was no significant correlation between initial serum cholinesterase levels and the need for ventilator support. **Conclusion:** No significant increase in serum cholinesterase levels with treatment in patients with poor prognosis and correlated with mortality. Serial measurement of PChE levels useful in predicting outcome and incidence of neurological complications.

Keywords: Organophosphorus; ventilatory support; severity; Peradeniya OP poisoning scale; serum cholinesterase level.

Introduction

Organophosphorus compound (OPC) poisoning has assumed alarming proportions with an annual incidence of over 3 million patients in 1990. Organophosphorus compound poisoning is primarily a problem of the developing countries [1]. Organophosphorus compound poisoning is the most common medico toxic emergency in India. Acute Organophosphorus compound poisoning is an

important indication for emergency admission in most hospitals throughout India [2]. Organophosphorus compounds were first developed by Schrader shortly before and during the Second World War. They were first used as an agricultural insecticide and later as potential chemical warfare agents [2]. Organophosphorus (OP) compounds are used as pesticides, herbicides, and chemical warfare agents in the form of nerve gases [2]. Its widespread use and easy availability has increased the likelihood of poisoning with these compounds. Although poisoning can result from occupational exposure or accidental ingestion, in most cases there is suicidal intent. Their common availability renders OP insecticide poisoning a worldwide health problem affecting millions of

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patients. India is a tropical country where agriculture forms the backbone of the nation. More than 60% of Indians are farmers. This being the fact, pesticides is the most frequent hazardous compounds that farmers are exposed to, OPC being most common in addition to the accidental intoxication from use of these compounds as agricultural insecticides; these agents are employed frequently for suicidal and homicidal purposes largely because of their easy availability at the moment of psychosocial or socioeconomic stress and low cost [3]. The WHO estimates that approximately 3 million pesticide poisonings occur annually worldwide and cause more than 220,000 deaths. Developing countries like India and Srilanka report alarming rates of toxicity and death [4]. Organophosphates act by irreversibly inhibiting the enzyme cholinesterase, resulting in accumulation of acetylcholine at synapses and myoneural junctions leading to cholinergic over activity. Direct cardio toxic effect of organophosphorus compounds is also reported [1,4]. Mortality ranges from 4-30% in Indian studies. Respiratory failure is the most common complication of OP poisoning leading to death. Early recognition and prompt ventilatory support may improve survival. Owing to limited availability of resources, all OP poisoning patients are not managed in ICUs in Indian setup. It is therefore important that clinical features and criteria to predict the need for ventilator support and complications be identified at initial examination. Serum cholinesterase levels are easier to estimate and usually depressed after OP poisoning. Peradeniya OP poisoning scale has not been studied much in Indian scenario. It could be a simple and effective system to determine the need for ventilatory support early on in the course. Hence this study was undertaken to assess the severity of organophosphorus compound poisoning both clinically by using Peradeniya scoring and by estimating serial serum cholinesterase levels serially and predicting prognosis, outcome and complications using cholinesterase levels.

Materials and methods

It is Prospective cohort study done at Tirumala Hospitals, Vizianagaram. Patients of acute organophosphorus poisoning admitted to the department of Medicine and Intensive care unit during the study period September 2014 to January 2016

Inclusion Criteria: Provisional diagnosis of acute organophosphorus poisoning irrespective age and sex based on history, physical and clinical examination

Exclusion Criteria:

1. Patients with multiple poisoning with other drugs such as opioids, diazepam, barbiturate etc.
2. Patients with history of respiratory diseases like bronchial asthma, cardiac diseases, neuromuscular diseases like myasthenia gravis or muscular dystrophy or other concomitant illnesses
3. Patients who receive treatment with atropine, before admission.
4. Patients who consumed alcohol

Patients who presented to emergency department with history of poisoning with known organophosphorus compound were taken as study subjects after considering inclusion and exclusion criteria. A detailed history, clinical examination and relevant biochemical investigations were performed. Patients were included in the study if they had a history of pesticide ingestion as indicated by patient or relatives, the referring doctor, or the pesticide bottle. A thorough clinical examination was carried out with particular reference to vital parameters, pupil size, assessment of central nervous system, respiratory system, cardiovascular system as per prescribed proforma. This examination took place during initial resuscitation and treatment of the patient. Peradeniya OP poisoning scale was applied to all study subjects and the severity of OP poisoning was graded as mild, moderate, severe. In all study subjects, 3 ml of plain blood was collected on admission before administration of atropine and PAM and plasma cholinesterase was estimated by colorimetric method.

According to cholinesterase activity the organophosphorus poisoning was graded as:

Cholinesterase activity	Grade of poisoning
> 50% (more than 50%)	Normal
20-50%	Mild
10-20%	Moderate
<10% (less than 10%)	Severe

All patients were managed with decontamination procedure including gastricavage. Intravenous atropine 2-4mg bolus and repeated every 5-15minutes

initially until atropinization. Drying up of secretions was taken as the end point of treatment.. The atropinization was maintained for 24-48 hours with

intermittent doses, every 1530.Minutes or depending on the need continuous intravenous infusion 0.02-0.08 mg/kg/hr, and then tapered over days depending upon patient's response. Pralidoxime chloride was given to all patients as 2g IV bolus over 10-15minutes immediately after admission and 0.5g-1.0g IV 4 th -12 th hourly depending on patient's condition. Patients were kept under strict observation during their stay in hospital. Assessment of patient's airway and need for endotracheal intubation was assessed. Patients with

respiratory failure were intubated and mechanical ventilator support was given. Psychiatric counseling was done for the patients who survived. The data were fed to the computer. The tabulations and the results for analysis were done with the help of SPSS (Statistical Package for Social Sciences) version 14,MINITAB version-16 and Microsoft Excel for Statistical measurements such as simple percentages, mean values etc., were used in the present study.

Results

The results of this study which included 80 patients were as follows

Table 1: Demographic distribution in study

Age intervals	Males	Females	Total
< 20 Years	11	14	25 (31.25 %)
20-30 Years	16	10	26 (32.5 %)
30-50 Years	20	7	27 (33.75%)
> 50 Years	1	1	2 (2.5%)
Total	48	32	80 (100 %)
Resident			
Rural	27	21	48 (60%)
Urban	21	11	32 (40%)

Age group ranged from 11 years to 55 years. (Mean 28.8±10.9 years). Majority of the patients were in the age group of 21-50 years which comprised 66.25% of the study patients. 60% of patients were males and 40% of the cases were females. Males were more than females in age group above 20 years. More than half of our study subjects (60%) were from rural area.

Table 2: Socioeconomic Status, Amount Poison and Mode of poisoning

Socioeconomic Status	No. of Patients and percentage
Lower	42 (52.5%)
Middle	30 (37.5%)
Upper	8 (10%)
Total	80 (100%)
Amount Poison in ml	
Less than 30 ml	33 (41.25%)
31-50	32 (40%)
More than 50	15 (18.75%)
Total	80 (100%)
Mode of poisoning	
Accidental	4 (5%)
Suicidal	76 (95%)
Total	80 (100%)

In this study, 52.5 % of patients were from lower socioeconomic group in contrast to 10% from upper class. More than 80% of patients had consumed less than 50 ml of poison. Only 18.75% had consumed more than 50 ml. (Mean 46.3 ± 31.5 ml). Almost all patients (95%) had consumed poison with a suicidal intent. In our study, only 4 patients had accidental poisoning.

Table 3: Presenting Symptoms and sign

Symptoms	No. of patients	Percentage
Bronchorrhea	10	12.5%

Headache	16	20%
Sweating	29	36.25%
Lacrimation	6	7.5%
Nausea	62	77.5%
Vomiting	50	62.5%
Breathlessness	44	55%
Salivation	29	36.25%
Diarrhea	29	36.25%
Sign		
Bradycardia	22	27.5
Tachypnea (RR >20)	59	73.75
Cyanosis	13	16.25
Creptitations	33	41.25
Fasciculations	52	65
Neck Muscle Weakness	20	25
Altered Sensorium	20	25
Seizures	7	8.75

The most common symptom reported by patients in our study was nausea (77.5%), vomiting (62.5%). Sweating was encountered in 36.258% and excessive salivation in 36.25%. In this study, the most commonly found clinical sign was tachypnea in 74% of Patients followed by fasciculations which was seen in 65% of patients.

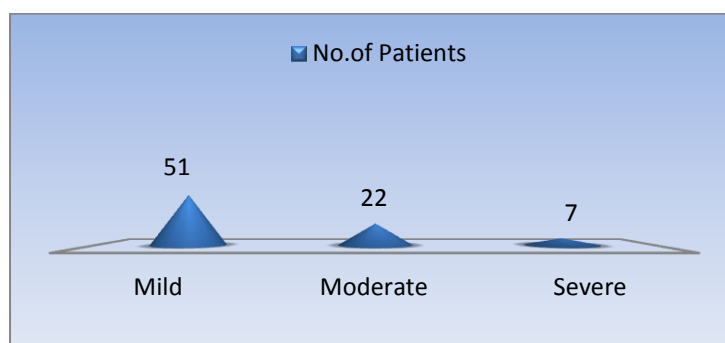


Figure 1: Graph showing severity of poisoning according to POP scale

63.75% of patients in our study belonged to mild grade of poisoning with a POP score less than 4. Only 7 patients had a score more than 7 and had severe poisoning.

Table 4: Correlation between time interval and severity according to PchE-1 levels between consumption to hospitalization vs. Outcome

Time Interval	Outcome		Total
	Survived	Expired	
Less than 2 hours	27	5	32
2-4 hours	30	8	38
more than 4 hours	9	1	10
POP scale			
Mild	46	5	51
Moderate	16	6	22
Severe	4	3	7
Severity according to PchE-1 levels			
Normal	11	0	11

Mild	24	3	27
Moderate	21	7	28
Severe	10	4	14

Most of the patients were presented within 4 hours after consumption (Mean time of presentation 2.48 ± 1.30 Hours). 84 % patients who presented to hospital within 2 hours survived. Mortality was high among patients who presented after 2 hours. 46 patients with mild grade of poisoning according to POP scale survived. While, only 5 patients expired. 27% of patients with moderate and 42% of patients with severe poisoning according to POP scale were expired. This was statistically significant ($p < 0.05$).

Table 5: Correlation between individual parameters of Peradeniya OP Poisoning scale with need for ventilatory support

Parameter	Score	Ventilatory support		Total	Significance	
		YES	NO		Chi Square	P Value
Miosis	0	2	3	5(6.25%)	4.6	0.1
	1	16	41	57(71.25%)		
	2	10	8	18(22.5%)		
Fasciculations	0	5	22	27(33.75%)	4.91	0.086
	1	22	29	51(63.75%)		
	2	1	1	2(2.5%)		
Respiratory rate	0	4	17	21(26.25%)	9.16	0.01
	1	15	31	46(57.5%)		
	2	9	4	13(16.25%)		
Bradycardia	0	17	41	58(72.5%)	4.34	0.114
	1	8	10	18(22.5%)		
	2	3	1	4(5%)		
Consciousness	0	17	43	60(75%)	6.52	0.038
	1	7	8	15(18.75%)		
	2	4	1	5(6.25%)		
Convulsions	0	23	50	73(91.25%)	4.47	0.034
	1	5	2	7(8.75%)		

$P < 0.05$ – significant

In our study except for MIOSIS and BRADYCARDIA all other parameters of POP scale have a statistically significant correlation with ventilatory support and can be used as predictors of ventilatory support and outcome.

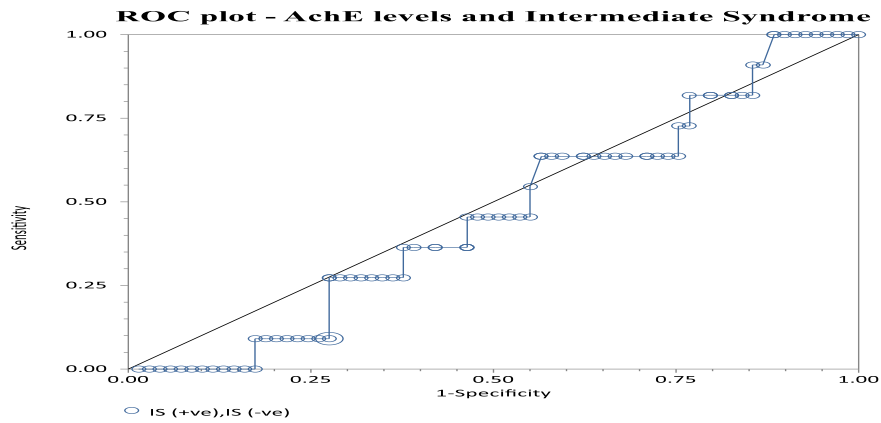


Fig 2 : ROC curve for initial PchE levels vs Intermediate syndrome

Sensitivity (95% CI) = 90% Specificity (95% CI) = 27%

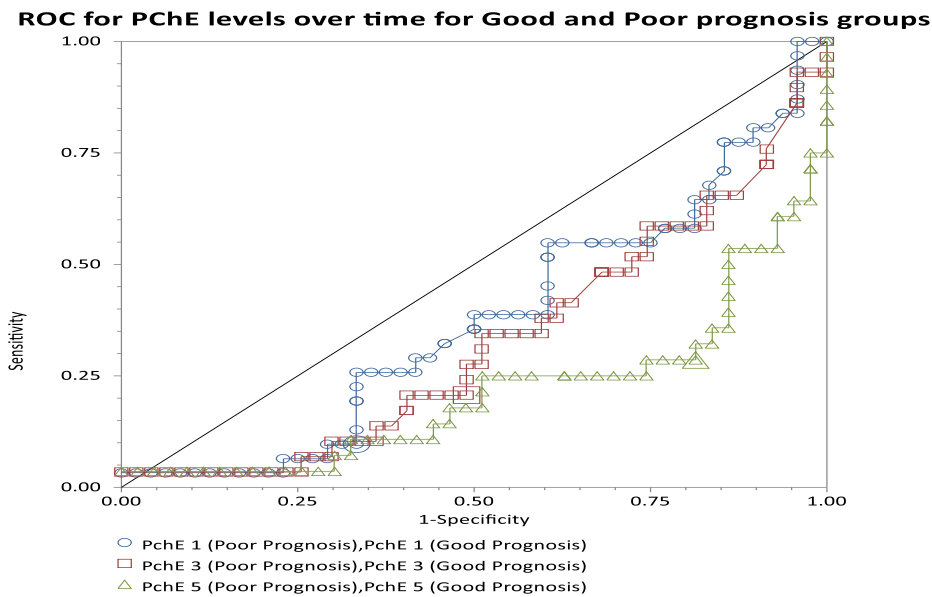


Fig 3: ROC curve for Serial PchE levels over time vs. prognosis

Table 6: Serial PchE levels over sensitivity and specificity

Parameter	Sensitivity	Specificity
PchE 1	90%	33%
PchE 3	79%	48%
PchE 5	71%	81%
PchE 1,3 and 5		

Discussion

The present study was conducted in Tirumala Hospitals, Vizianagaram from September 2014 to January 2016. A total of 80 cases were studied. The clinical and diagnostic findings of this study are compared with our studies in literature here.

Age of patients: In our study, majority of patients were in the age group of 30-50 years (34%). 66.25% of patients were within 50 years of age. This is in comparison to studies done by Rehiman et al[5], Goel et al[6], Doshi et al[7], and Noura et al[8].

Gender distribution: This study revealed a male preponderance (60%), females accounting for 40% of cases. The male to female ratio in this study is 1.5:1. This corresponds to gender distribution reported by Shankar et al[9] (1.48:1), A Goel et al[6] (2.5:1), Gupta et al[10].

Socio economic status: 52.5% of patients in this study were from a lower socio economic group. This is in comparison to study done by A Goel et al[6] and Chatterjee et al[11], who found that 75% of patients were from low socioeconomic group.

Intention of poisoning: Almost all cases in our study (95%) had consumed poison with a suicidal intent. As OP compounds are generally available ready hand as pesticides and open access to these compounds at pesticide shops may be the reason for OP compounds to be used as a common mode of suicidal attempt. This is in comparison to values reported by Rehiman et al [5], Noura et al[8](90%), Goel et al(6) (96.1%), and Gupta et al[10](91%).

Quantity of poison consumed: About 80% of our patients had consumed less than 50 ml of poison and 20% had consumed more than 50 ml. In this study we observed that both the severity and mortality were significantly higher (11.25%) in those patients who were hospitalized more than 2 hours after exposure, compared to the mortality of 6% in patients who were hospitalized within 2 hours of exposure. These findings are in correlation with findings by Gupta et al[10], Arup kumar kundu et al[12]. In the present study nausea was the commonest symptom seen in 78%, followed by vomiting (62%) and sweating in 36%. Convulsions were seen in 8.75% of patients. These observations were comparable to the pattern reported by Rehiman et al[5], and Goel et al[6]. All patients included in this study had a characteristic smell of organophosphorus compound. The common clinical signs were miosis (76%), tachypnoea (74%), Fasciculations (65%). These results are comparable to the studies of Rehiman et al [5], A Goel et al[6] and APN Kumar et al[12].

Quantity of poison consumed and mortality: In our study, about 33 patients had consumed less than 30 ml of poison. Most patients in this group had mild (60%)

and moderate grade (27%) of poisoning according to Peradeniya OP Poisoning (POP) scale. 24% of patients who had consumed less than 30 ml had severe poisoning according to PChE levels. As the amount of poison increased to more than 50 ml, severity of poisoning did not correlate with either PChE levels or POP scale. (p Value 0.141 and 0.706 respectively) Total mortality and poisoning: Our study had a mortality of 17.5% which is in comparison with Das.B.W[13] et al(13.3%), Arup kumar kundu et al[12](13.3%), Noura et al[8] (10%), Rehiman et al[5] (14%). Most deaths in our study occurred within 24 hours of admission to hospital. Delay in hospitalization, type of poison and higher clinical score at presentation accounted for mortality. 90% of patients with mild grade of poison according to POP scale survived. 9 out of 14 patients who had expired had moderate grade (6 Patients) and severe grade (3 Patients) according to POP scale. POP scale had a statistically significant correlation with mortality. (p value < 0.036). There is no significant correlation between initial pseudocholinesterase levels and outcome of the patients. (p Value 0.146). This is in contrary with findings from Namba et al[14] who found definitive correlation between PChE levels and severity of poisoning and considered it a valid marker of severity and to prognosticate patients with OP poisoning. There is a significant correlation between outcome and serial measurements of PchE levels. In patients who were survived there is highly significant increase in PchE levels from Day 1 to Day 5 (p < 0.001). But in those who were expired there is no significant increase. (p > 0.05). This is in accordance with Ayugan and et al[15].

Ventilatory support : Respiratory failure requiring ventilatory support was observed in 35% of patients in our study. This is in comparison to values obtained by Noura et al[8] (40%), A Goel et al[6] (34.95%), Thomas chang et al[16](40.2%).

Pseudocholinesterase levels: PChE levels were assessed in all patients at admission to hospital and on Day 3 and Day 5. It was classified according to Proudfoot[17] classification into subclinical (normal), mild, moderate and severe poisoning. In our study 13.75% of patients had subclinical poisoning and 17.5% had severe poisoning. 90% of patients with normal grade of poisoning did not require ventilatory support. 4% of patients with <50% required ventilatory support. But in our study there is no significant correlation between PchE-1 levels and the need for ventilatory support. Weissmann- Brenner et al [18] found a direct correlation between the degree of inhibition of PChE levels and the severity of

poisoning. Similar findings were observed by S.D.Zawar et al[19]. Ayugan and et al[15] found there is no significant correlation between initial PchE levels and Severity of Poisoning. So it can said that, PchE-1 levels cannot be a predictor to categorize patients who might require ventilatory support at admission. However serial measurements of PchE levels on day – 1,3 and 5 can predict poor prognosis group who may require ventilatory support.

Peradeniya OP poisoning scale:POP scale was calculated for all patients on admission. 64% of patients had mild grade of poisoning and 27% had moderate grade of poisoning. 7 patients in our study belonged to severe grade of poisoning according to POP scale. The individual components of POP scale namely miosis, fasciculation, respiratory rate, Bradycardia and level of consciousness were compared with need for ventilatory support.

Miosis:Miosis was seen in 93% of patients of OP poisoning in our study. 28% of patients who had pupil <2 mm required ventilatory support where as 55% of patients with pinpoint pupil required ventilatory support. But it had no statistical significance in predicting the need for ventilatory support. This is in contrast to findings by A Goel et al[6] who found statistical significance of miosis in predicting the need for ventilatory support. 64.7% of patients with pupil <1mm required ventilatory support.

Fasciculations : Fasciculations were seen in 53 out of 80 patients, of which 65% of patients did not require ventilatory support. One patient who had generalized fasciculations required ventilatory support. This did not have statistical significance in predicting the need for ventilatory support. A Goel et al(6) found that patients with generalized fasciculations required ventilatory support more frequently than individuals with absent or only localized fasciculations.

Respiratory rate :60% of patients in our study had tachypnea and 40% required ventilatory support. All patients who had presented with respiratory rate more than 20 with central cyanosis required ventilatory support. This had a significant (p 0.01) correlation in predicting the need for ventilatory support. A Goel et al(6) and Bardin et al[4] has found a significant correlation between respiratory failure and need for ventilatory support.

Bradycardia :This was seen among 22 of 80 patients (27.5%). Among them 50% required ventilatory support. 75 % patients who had a POP score of 2 for Bradycardia required ventilatory support.29 % patients who didn't have bradycardia required ventilatory support. Bradycardia scoring doesn't correlated significantly in predicting the need for ventilatory support. p value (0.114)

Consciousness and Convulsions:In our study impairment of consciousness was seen in 20 patients, of which 55% required ventilatory support. 71% of patients who had convulsions at presentation required ventilatory support. This had a statistical significance in predicting the need for ventilatory support. A Goel et al[6] have reported that 74% of patients with lower Glasgow coma scale required ventilatory support.

Peradeniya OP poisoning score:POP score ranges from minimum 0 to maximum 11. In our study only 8 of 51 patients (15.6%) with mild grade of poisoning required ventilatory support. Among patients with moderate and severe poisoning 14 out of 29 patients required. 48% of patients with POP score more than 4 required ventilatory support. This was statistical significant in predicting the need for ventilatory support. Rehiman et al[5] found out a significant association between POP score and PChE levels, POP score and hospital stay, total dose of atropine required, mechanical ventilation. The higher the score of POP scale, higher was the suppression of PChE levels. A Goel et al[6] compared individual components of POP scale and concluded that they can be used in predicting the need for ventilatory support. In our study there is no statistically significant correlation between severity according POP scale and severity according to initial pseudocholinesterase levels in contrary to Rehiman et al[5]. So it can said that, POP score can be a used as predictor to categorize patients who might not require ventilatory support at admission but not PchE -1 levels. However as mentioned earlier, studies with a large sample size and a heterogeneous population have to conducted to confirm the results.

Serial Pseudocholinesterase levels and Prognosis : There is no significant correlation between the initial pseudocholinesterase levels with prognosis of patients. But, with serial estimation of pseudocholinesterase levels over time prognostification of acute organophosphorus poisoning can be done to foresee the complications like intermediate syndrome and need for ventilatory support.

Conclusion

The patients were in the age group of 11 to 55 years. Majority of the patients were in the age group of 21-50 years (66.25%). 60% of the patients were from rural areas and most of them were agricultural workers.52.5% of patients were from low socio economic stratum. Route of intake of poison was oral in majority of patients. 95% of patients consumed poison with a suicidal intent. Mortality was less among the patients who presented to the hospital early as compared to those who presented late. Amount of

poison consumed did not correlate with the severity of poisoning. The most common symptom reported by patients in our study was vomiting (62.5%). The most commonly found clinical sign was tachypnoea in 73% of patients followed by fasciculations which was seen in 65% of patients. In our study mortality was 17.5%. 63% of patients in our study belonged to mild grade of poisoning with a POP score less than 4. Only 7 patients had a score more than 7 and had severe poisoning. The POP scale and serial estimation of pseudocholinesterase levels showed a significant association in predicting the poor prognosis group (Intermediate syndrome, ventilatory support and mortality). Lower grade of poisoning and those with significant mean increase in pseudocholinesterase levels over time had a better outcome whereas higher severity of poisoning and those with no significant mean increase in pseudocholinesterase levels over time had a poorer outcome.

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