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Original Research

Prognostic value of c-reactive protein in organophosphorous poisoning

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ABSTRACT:
Introduction: Organophosphorous compounds used worldwide as pesticides and it easy availability has led to an increase in the incidence of both intentional and accidental poisoning of the same. The incidence is slightly more in the developing nations. Easily available biomarkers which can be made available in rural setups; which help in determining the severity of organophosphorous poisoning is currently the need of the hour. **Aim**: To study the usefulness of C - reactive protein (CRP) levels in determining prognosis in patients of acute organophosphorous poisoning**. Settings and design:** This is a prospective, observational study done in a single setting in a tertiary care center in coastal Karnataka. **Materials and methods**: All patients who had a history of consumption/contact of organophosphorous compounds, clinical features characteristic of organophosphorous compound poisoning and those patients having response to treatment with oximes and atropine during the study period of one year were included in the study. Cases of carbamate poisoning, obese patients, smoker, history of allergy, history of recent trauma, surgery or burns, features suggestive of sepsis on admission, known cases of cancers, known cases of autoimmune diseases, history of recent myocardial infarction were the exclusion criteria. **Statistical analysis:** All categorical and continuous variables were presented as mean±standard deviation and median with interquartile distance (Q1-Q3), where required. Mann- Whitney *U* test was used to analyze the difference between the means of two groups (CRP negative cases and CRP positive cases). Chi square tests were used to analyze the categorical variables. **Results**: Among the 30 patients studied, parathion was the most commonly used organophosphorous compound. 43% of patients had elevated C-reactive protein levels. 46% among these patients required intubation and mechanical ventilation whereas none of the patients with normal C-reactive protein levels required mechanical ventilator supports ($p<0.05$). **Conclusion**: Elevated serum C-reactive protein level has good correlation with severity of poisoning and it can be used as alternative index for severity assessment of organophosphorous poisoning.
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INTRODUCTION

Today, organophosphorous compounds are used all over the world in agriculture as well as in various household gardens. The easy availability of these pesticides has resulted in an increase in accidental and suicidal poisoning, especially in the developing countries. This may also be because of easy accessibility over them as many of these countries allow the sale of organophosphates directly over the counter and have inadequate regulations over their usage and appropriate storage. [1,2]

In 2012, according to WHO data, around 193,460 people died worldwide from unintentional poisoning. Among these, 84% occurred in developing and under-developed countries. [3]

In Africa and the far east, the widespread use of OP compounds has resulted in increase in poisoning because of easy availability, indiscriminate handling and storage and also because of lack of knowledge concerning the serious consequences of poisoning. The environmental protection agency reported that over 80% of all hospitalization in the US from pesticide poisoning were due to the organophosphate mostly involving children, farmers and skilled and unskilled laborers. [4]

A high incidence has been reported from Japan, Finland, Denmark, California and Florida in the past, the greatest being in Japan where there were 19,436 cases of organophosphate poisoning in 17 years. [5]

In India organophosphates are among the commonest poisons used for suicide. [6] Singh S et al. [7] and Adlakhs A et al. [8] have reported organophosphates ad the second most common poison in their studies in Chandigarh and Punjab respectively. Kamath et al. [9] reported that diazinon was the most common source of poisoning in Bombay. In a study done in Manipal, it was found that organophosphates were the most common source of poisoning in the region. [10]

The two principal human cholinesterases are acetyl cholinesterase and pseudocholinesterase. Acetylcholine esterase (true choline) is primarily in nervous tissue and erythrocytes; pseudo cholinesterase is found in the liver and serum. The organophosphates are powerful inhibitors of the cholinesterases and often act by irreversibly binding phosphate radicals of the organophosphate to the active sites of the enzymes, forming phosphorylated enzymes. [1,2] The toxicological effects of the organophosphate are almost entirely due to the inhibition of acetylcholinesterase in the nervous system, which results in the accumulation of acetylcholine at synapses and myoneural junctions. Thus organophosphates poisoning is more accurately assessed in the lab by measurement of the red cell (true) cholinesterase rather than the serum (pseudo) cholinesterase. [1,4,5]

The excess of acetylcholine initially excites and then paralyzes transmission in cholinergic synapses which include the central nervous system, the parasympathetic nervous system and a few other nerve endings such as the sweat glands which cause the muscarinic effects, in the somatic nerves and the ganglionic synapses of autonomic ganglia which causes the nicotinic effects. The clinical features of organophosphate poisoning are thus an expression of these effects caused by the overabundance of acetylcholine. [1,2,4,5,11]

Organophosphate poisoning seems to occur in different circumstances. A study from Texas demonstrated that organophosphate poisoning often occurs in children usually as a result from inappropriate and unnecessary storage of pesticides in households all through the year. [1,4] Many people are exposed to the compounds often unintentionally and subclinical poisoning may occur in around 20-41% of people who work with or come into contact with the compounds. [1]There have been instances of poisoning after ingestion of food sprayed with one of the more persistent insecticides in which cases there hasn't been sufficient time for the hydrolysis of the insecticide. Incidence of mass poisoning by gross contamination of food has been reported from India, Egypt, Singapore and Mexico. [5] A graphic example is provided by the Kerala food poisoning case of 1958, in which over a hundred people lost their lives after consuming wheat, sugar, etc. that had been stored in the same area as packages of folido (Parathion). [6] However, suicidal attempts account for the largest number of organophosphate poisoning, the commonest being oral ingestion. [1,5,6] Poisoning by injection is rare, but 10 cases have been reported. [5]

The time interval between the exposure and onset of symptoms varies with the chemical, route of entry, degree of exposure and always occurs within hours of exposure. [1,5,6] Symptoms first may suggest mild poisoning but may rapidly progress to indicate severe poisoning. The clinical features may be due to muscarinic effects like sweating, salivation, lacrimation, urinary incontinence, diarrhea, abdominal cramps, vomiting, miosis, wheezing, bradycardia and blurring of vision. Also, nicotinic effects like fasciculation, cramps, respiratory distress, tachycardia, elevated blood pressure, anxiety, convulsions, circulatory depression etc. can be seen.

Initial symptoms usually include headache, intestinal cramping, vomiting, diarrhea, dizziness, weakness, excessive sweating and salivation.

There are more than 250 brand names registered as organophosphate pesticides. These compounds are classified as highly toxic compounds like Octamethyl pyrophosphoramide (OMPA), Tetraethyl Pyrophosphate (TEEP), Parathion, Phosphamidon etc. and moderately toxic compounds like Dichlorvos (DDVP), Quinalphos, Fenthion, Diazino, Fenitrothion, Malathion, Temephos etc. Highly toxic compounds like parathion which even when instilled into the eye or when allowed to stay on the skin can prove fatal. [6]

A criterion for the diagnosis of OP poisoning has been proposed using a combination of clinical manifestation, a decrease in the pseudo cholinesterase or red blood cell cholinesterase activity and the response to treatment. Combination of these different criteria serves to differentiate other conditions such as infections, metabolic derangements (hypoglycemia, uremia) and acute neurological conditions as well as other types of poisoning. However, it may be difficult to distinguish from other poisonings especially opiates, mushroom poisoning, nicotine poisoning and venomous snake bite. In these cases, a careful history and physical examination will aid us in establishing a diagnosis. [1,2,4]

A generally known and accepted sign of organophosphorous poisoning which aids in early diagnosis has been that of extreme miosis (pinpoint

pupils) which is because of parasympathetic stimulation of the iris which is in turn, due to the inhibition of the enzyme cholinesterase. [12] Dixon, Wenatche, Wash reported 2 cases which represent instance of severe poisoning from the organophosphate insecticide parathion, in which miosis did not occur early in the illness which lead to a delay in diagnosis and hence a delay in initiating the treatment. [13]

Measurement of the serum pseudocholinesterase activity is the most valuable special investigation to assess suspected poisoning. The activity is invariably decreased on organophosphate poisoning and the sensitivity is close to 100% for cases with significant poisoning. [1] However, a point to note here is that there has been no conclusive evidence for association of magnitude of the decrease of the enzyme levels and the severity of poisoning. In one study fasciculations were the only finding which showed correlation with pseudo cholinesterase being noted in 57% of patients with pseudocholinesterase levels below 20 units. After treatment with atropine there is no correlation between symptoms and pseudocholinesterase level at al. [1,14] Specific organophosphate compounds can be identified with the help of high profile liquid chromatographic methods. This is usually not of much clinical or therapeutic value because the mainstay of the treatment is to control the cholinergic over activity caused by these compounds and is not individualized for the particular type of compound. [1,2,4,15]

Death can occur early (within 24 hours) after complications arise in untreated cases and within 10 days in those who receive optimal treatment. Early deaths are chiefly related to depression of the central nervous system, seizures, ventricular arrhythmias or respiratory failure which may be because of bronchospasm, aspiration of gastric contents, pulmonary edema, respiratory muscle paralysis or apnea due to central cause (depression of the medullary respiratory center.) [1] Late mortality is usually caused by respiratory failure often due to infections or complications related to prolonged mechanical ventilation and intensive care management. However, even in the later days of the illness, ventricular arrhythmias, sudden collapse and death may occur. [1,2,4] Type II paralysis first described by Wadia et al. [16] in 1974 and later christened Intermediate Syndrome by Senayake [17] has been reported in Indian and western literature. The exact mechanism of this neurotoxic syndrome is poorly understood. Godoth Et et [18] postulated that the release of previously inactivated cholinesterase inhibitors acting specifically on nicotinic receptors caused this syndrome. Seneyake reported 10 cases with intermediate syndrome despite early administration of PAM. [17] Samuel J et al noted the incidence of intermediate syndrome as 47%. Of these 61% received a 4-day continuous infusion of 12 gm and 39% received a single dose of 1 gm of PAM. [19] Both hyperglycemia as well as hypoglycemia have been reported as acute manifestations. [4,5,20] Delayed complications are usually related to CNS and peripheral neuropathies; these include reports of GB syndrome and late onset paralysis. Peripheral neuropathy is considered rare. [21]

MATERIALS AND METHODS

Patient Population

The study was conducted from August 8th 2007 to August 29th 2008 at our tertiary care center after obtaining permission from the Institutional Ethics Committee (IEC: 375/2007). The work was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Informed consent was obtained from all the participants. A total of 30 patients of all age groups and both the genders have been taken into the study. Inclusion criteria involved history of consumption or contact with OP compounds and clinical features characteristic of OP poisoning, response to treatment with atropine and oximes in cases where the history of the type of compound consumed is not available. The exclusion criteria included cases of carbamate poisoning, obese patients, smoker, history of allergy, history of recent trauma, surgery or burns, features suggestive of sepsis on admission, known cases of cancers, known cases of autoimmune diseases, history of recent myocardial infarction.

Informed consent was obtained from all the participants.

Ethical Considerations

All invasive procedures were done after taking informed consent either from patient or patient's attender. No investigation was done without recommendation from treating team

Data Collection

These individuals are subsequently analyzed thoroughly as per protocol which included a detailed clinical history and a complete physical examination followed by baseline and specific laboratory tests including c-reactive protein levels and follow up of patients to determine nature of outcome and to see if it is related to c-reactive protein levels.

Cases of organophosphorous compound poisoning were confirmed by aspiration of gastric contents and analysis in the biochemistry laboratory. Also simultaneously, serum pseudocholinesterase levels were measured. Levels below 5320 U/L was taken as significant

Laboratory methods

Organophosphorous compound poisoning was confirmed by aspiration of gastric contents and analysis in the biochemistry laboratory.

Normal pseudocholinesterase levels were taken as 5320-12920 U/L.

Normal serum C Reactive Protein levels were taken as those between 0-5mg/L. Levels below 5 mg/dL was considered negative
CRP was measured by the lactate- pyruvate method using Roche Cobas c system.

Statistical analysis
All categorical variables like gender, clinical features etc. were analyzed and reported in the form of frequency and percentages and continuous variables like duration of ICU stay were presented as mean±standard deviation and median with interquartile distance (Q1-Q3), where required. Mann-Whitney *U* test was used to analyze the difference between the means of two groups (CRP negative cases and CRP positive cases). Chi square tests were used to analyze the categorical variables. Data was analyzed using SPSS 16.0 (IBM SPSS statistics, USA) software

Management of cases of organophosphorous poisoning
A thorough history was taken on admission. Airway, breathing, circulation was maintained. Intubation and mechanical ventilator assistance was given, when necessary. Bolus dose of injection atropine 1-3mg was given along with repeat doubling doses if necessary. Injection pralidoxime 2 g intravenously over 20–30 minutes into a second cannula; followed by an infusion of pralidoxime 0·5–1 g/h in 0·9% normal saline was given. This was done according to the institutional policy of treatment of OP poisoning. These cases were monitored constantly throughout their duration of stay in the hospital. The need for intubation and mechanical ventilation, the duration of ICU stay and mortality, if any, was noted. The cases were categorized as mild, moderate and severe according to the criteria shown in **Table 1.**

Table 1 Peradeniya organophosphorus poisoning (POP) scale [22]

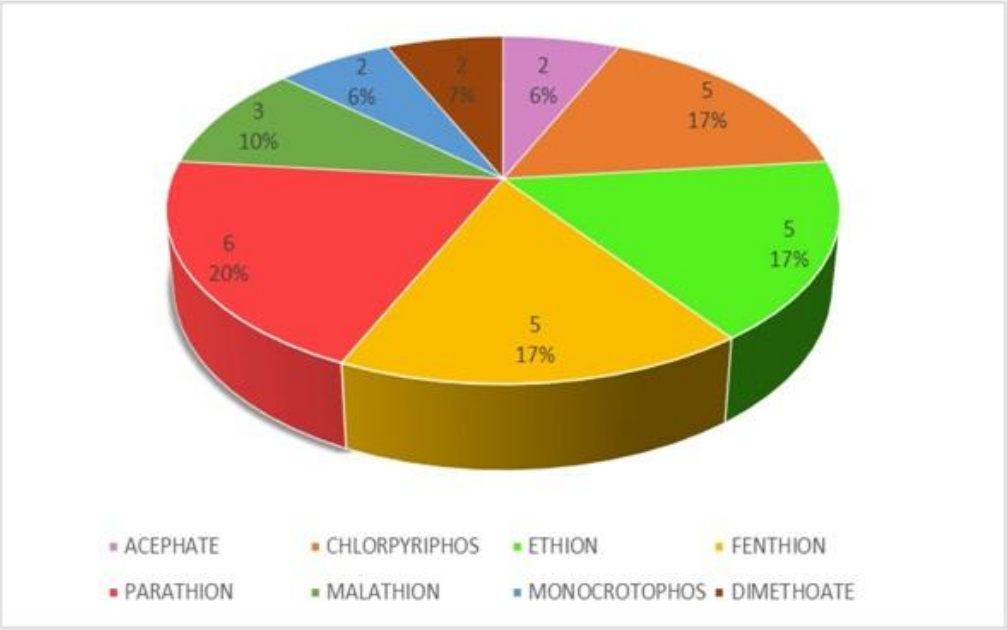
Parameter	Criteria	Score
Pupil size	≥2 mm	0
	≤2 mm	1
	Pin-point	2
Fasciculation	None	0
	Present but not generalised or continuous	1
	Generalised or continuous	2
Respiration	Respiratory rate ≤20/min	0
	Respiratory rate >20/min	1
	Respiratory rate >20/min with central cyanosis	2
Bradycardia	Pulse rate> 60/min	0
	Pulse rate 41-60/min	1
	Pulse rate ≤ 40/min	2
Level of consciousness	Conscious and rational	0
	Impaired, responds to verbal commands	1
	Impaired, no response to verbal commands	2
Seizures	Absent	0
	Present	1
0-3: mild poisoning, 4-7: moderate poisoning, 8-11: severe poisoning		

RESULTS

Demographic Characteristics

Here, we report the characteristics of the 30 patients, 15 males and 15 females, admitted with organophosphorous poisoning from August 8th 2007 to August 29th 2008 and treated at our center. The type of organophosphorous compound consumed has been shown in **Figure 1**.

Fig 1. Type of organophosphorus compounds consumed



The mean age of the patients admitted was 30.66±13.19 years.

Table 2 Baseline characteristics of the patients admitted with organophosphorus poisoning

Age (years)	**Male [*n* (%)]**	**Female [*n* (%)]**
<20	1 (6.7)	6 (40.0)
20-30	8 (53.3)	4 (26.7)
30-40	2 (13.3)	2 (13.3)
40-50	2 (13.3)	2 (13.3)
>50	2 (13.3)	1 (6.7)
Classification of severity using the Peradeniya organophosphorus poisoning (POP) scale [*n* (%)]		
Mild	6 (20.0)	
Moderate	15 (50.0)	
Severe	9 (30.0)	
Serum CRP [*n* (%)]		
Positive	13 (43.3)	
Negative	17 (56.7)	

Table 2 shows the baseline characteristics of the patients admitted with OP poisoning and treated.

Fig 2. Clinical features of patients presenting with organophosphorus poisoning

(A) Muscarinic effects (B) Nicotinic effects

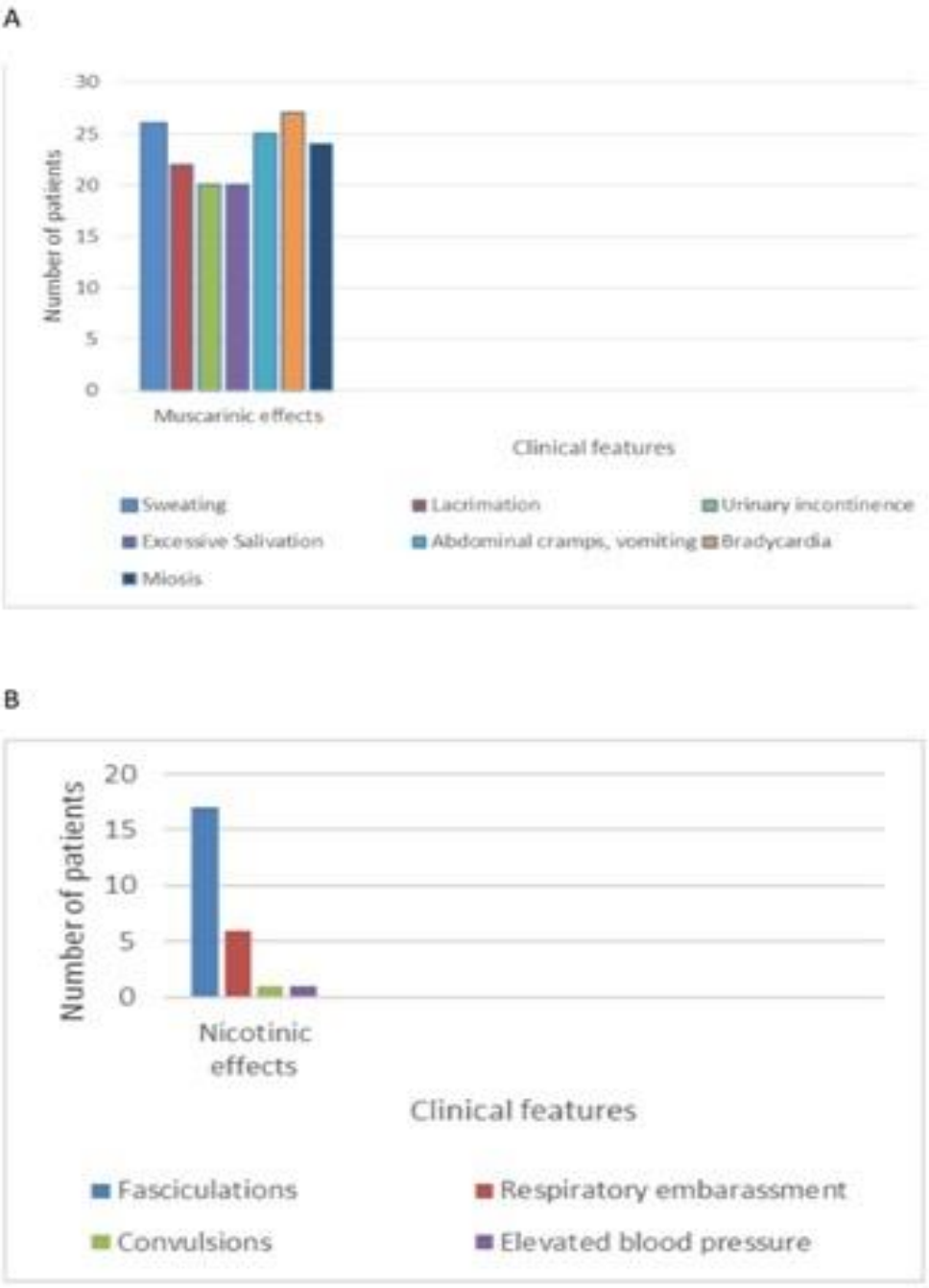


Figure 2 shows the clinical features of patients of organophosphorous compound poisoning. Initially the symptoms due to muscarinic effects predominate. Later symptoms due to nicotinic effects can be seen in some patients. It should be noted that since a patient can have more than one symptom at presentation, an overlap of the same, in the table was unavoidable. Among these, 29 cases were intentional self-harm while 1 case was that of accidental contact poisoning. 6 patients out of 30 required intubation and mechanical ventilation. Interestingly, it was noted that the CRP levels were increased in patients who had consumed highly toxic substances like monocrotophos, parathion etc. A total of 6 patients (20%) required intubation and mechanical ventilation. There were 3 deaths (1%), out of which 2 patients had consumed monocrotophos who later on developed multi organ dysfunction and the other patient developed respiratory failure.

The serum CRP levels were measured and cases categorized into two categories as those with positive CRP levels and negative CRP levels. These categories were further compared against various variables as shown in **Table 3**.

Table 3 Comparison of CRP positive and negative patients with various variables in organophosphorus compound poisoning

Variable		Serum CRP		p value
		Positive	Negative	
Ventilator requirement [a] [*n* (%)]	YES	6 (20)	0 (0)	0.025*
	NO	7 (23.33)	17 (56.66)	
Mortality [a] [*n* (%)]	YES	3 (10)	0 (0)	0.371
	NO	10 (33.33)	17 (56.66)	
Duration of ICU stay (days) [b]	8.69 ±4.26		6.47±2.45	0.083

*Statistically significant values

[a] Data subjected to Chi square test and [b] data subjected to Mann Whitney U test expressed in mean±standard deviation

DISCUSSION

In our study of thirty cases, we found that the maximum incidence of cases was seen in the age group of 20-30years age group. Similar findings were found by Shah NM and his colleague in their study of 50 cases of organophosphorous poisoning in Rajkot, India and also Kora SA and his colleagues in their study on 148 cases of organophosphorous poisoning in India. [23,24] Emerson GM and his colleagues, in Australia, however, in their study, found that the incidence was more in the 30-50year age group. [25] In this study, there was 1:1 ratio of males: female population. There was a similar finding in the study done by Kora SA in which the female population was 52.8% and the rest were males. Banerjee I and his colleagues, in their study showed a male: female ratio of 1:1.38. [26] However, Emerson GM in their study, showed a predominance of males in their study. [25] In India, many cultural and socio-economic factors come into play. There is an age-old tradition in India, where a woman, after her marriage, leaves her parents' house and stays with her in-laws. Though cases of early marriage and cultural practices like dowry are reducing, these may be the additional stressors for women of this age-group, which might be one of the additional factors for intentional self-harm.

Our study showed that a majority of cases were of intentional self-harm and a maximum of compounds like parathion, chlorpyrifos and fenthion were used for the purpose. Banerjee I in their study showed that Methyl parathion was the most common poison consumed by the patients (35.74%) followed by diazinon, chlorpyriphos, dimicron. [26] In a study conducted in Nepal by Rehiman S and colleagues, methyl parathion (64.62%) was the most common one followed by Baygon spray, malathion and dichlorvos. [27] Methyl parathion was also the most common poison in studies conducted in Chennai by Shivakumar S and colleagues. [28] However, in a study conducted in Turkey, dichlorvos was the most common one used. [29] The compound, however, depends on the type of insecticide used and available in abundance, in the local area.

Our study had a predominance of muscarinic features, of which, symptoms like nausea and vomiting topped the list. Next symptom which predominated was abdominal pain and loose stools. Miosis and bradycardia were the most common signs seen. Similar findings were seen in the Indian study done by Banerjee I and colleagues where nausea and vomiting were the most common symptom (85.02%) while miosis (91.94%) was the most common sign seen. [26] Shah NM and colleagues, in their study, noted that nausea and vomiting was the most common symptom. Miosis was present in 70% of cases in their study. [23] However, a number of reports have indicated that miosis is not a constant finding in animals or man after sufficient exposure to a number of organophosphate compounds to produce systemic effects. [12]

Our study showed 1% mortality with two patients having multiorgan failure and one patient developing respiratory failure. The mortality rate in the study done by Kora SA [24] was 4.72% and Banerjee I and colleagues [26] was 5.78%. However, the Turkish study had a mortality rate of 9.1%. [28] Shah NM and colleagues observed that mortality rate was higher in patients with ARDS (100%), followed by type-II paralysis (80%), sudden cardiac death (75%), and acute respiratory failure (62.5%). [23] The vast exclusion criteria has screened various comorbidities like COPD, obesity from our study which might be the reason for the lower mortality rate in our study.

Our study showed significant association with the requirement of ventilator supports and indirectly, the severity. A case control study done by Wu X and colleagues showed patients with severe acute organophosphorous poisoning exhibited increasing

plasma CRP and copeptin contents over time (P<0.01), while patients with mild and moderate poisoning exhibited reduced plasma CRP and copeptin contents over time. [30] Another study from Taiwan by Tsai RR and colleagues showed similar results. [31]

CONCLUSION

43% of the study population had elevated serum C-reactive protein levels. Very high serum C-reactive protein levels were seen with poisoning with highly toxic substances like monocrotophos, parathion etc. Elevated serum C-reactive protein levels had significant association with requirement of mechanical ventilator support. However, these C-reactive protein levels did not correlate well with mortality. So we conclude that elevated serum C-reactive protein level has a good correlation with severity of organophosphorous poisoning and requirement of mechanical ventilation.

Our study is unique as correlation of CRP with organophosphorous compounds has not been studied extensively, especially in our country. Since CRP is a widely and easily available tool, it helps in easy triaging of cases at admission. Using this tool, rural hospitals with small setups can triage the patients to tertiary care centers, if necessary. A large number of confounding factors have been removed with some large exclusion criteria. Hence this study has added value.

The limitation of our study is that it is done in a single-center. Maybe a larger sample size will help us in getting a better picture in the use of CRP in OP compound poisoning.

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