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CARDIAC MARKERS IN ACUTE ORGANOPHOSPHOROUS POISONING

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ABSTRACT

Background: Organophosphorous (OP) compound poisoning is a common toxological emergency in agricultural country like India, as it is easily available. Cardiac Marker (CPK-MB &Trop-I) level were frequently elevated in OPC poisoning and ECG changes were observed. Fatality is mostly due to cardiovascular and respiratory failure.

Aim & Objective: To study clinical severity and it's correlation to myocardial injury in respect to Troponine-I, CPK-MB and ECG changes.

Material and Methods: A prospective observational study conducted among 97 patients admitted in Medicine Department, VIMSAR, Burla with history of OPC poisoning during the period of Dec 2019 to Dec 2021 after approval from institutional Ethical Committee. Changes in ECG, Serum CPK-MB, Trop-I level were estimated by IFCC and ELISA method, respectively and observed at admission, after 3 days and at discharge.

Results: Mostly Chlorpyriphos (23.7%) was consumed followed by Phorate (22.7%). The most common clinical symptoms was bradycardia (49.5%) followed by hypotension (26.8%), and tachycardia (21.6%). Acetylcholine esterase level decreased (<25000IU) in 75.3 % patients. ECG showed Sinus bradycardia (44.3%), followed by QT prolongation (33%). On day3, significantly elevated Trop-I (27.80 %) and CPK-MB(29.89%) were found.

Conclusion: Majority of the patients were in the age group of 45-60 with males more than females. Occurrence of cardiotoxicity was related to the type of compounds ingested. Elevated CPK- MB and Trop-I indicates severity of OPC poisoning requiring longer ICU stay and also statistically significant to predict the prognosis of poisoning.

Keywords: Organophosphorus compound, Poisoning, ECG, Cardiac Markers.

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INTRODUCTION

Organophosphorus (OP) pesticide self-poisoning is estimated to kill around 200000 people each year, largely in the Asia-Pacific region. This predominantly occurs in rural communities and is often an impulsive act of self-poisoning with medication in the West; the critical difference being the 10–20% case fatality rate (for example, compared to 0.3% in Britain).[1] OP poisoning is also of great interest to developed countries vulnerable to terrorist or military attack with nerve agents. As per National Crime Records Bureau report (2016), 27.9% of suicides were committed by consuming poisons in India in the year 2015 [2] Out of all pesticide related deaths, poisoning with Organophosphorus compounds accounted for two-thirds of all the deaths [3]. The principal pharmacological action of all OPs is the inhibition of acetyl cholinesterase that leads to respiratory failure. However, there is much variation in the time of onset and clinical features depending on the particular OP compound involved. OP poisoning has high inpatient mortality, mainly cardiorespiratory arrests after admission which is similar to study done by Eddleston M et.al. (38% of patients requiring intubation).[4]

Cardiac complications are common and can be fatal if not diagnosed and treated early. The exact pathogenesis of cardiac complications has not yet been defined. A few important studies have been carried out both in India and abroad to study the cardiac complications and ECG changes in OP poisoning. The current study was carried out to understand the cardiac manifestations of OP poisoning with special reference to cardiac enzymes.

AIMS & OBJECTICES

1. To study the clinical profile of myocardial involvement in various OP compound poisoning.
2. To study prevalence and predictors of outcomes of myocardial injury with Trop-I, CPK-MB as Cardiac biomarkers and ECG changes in Organophosphorus poisoning.

METHODS

Patients with history of OP poison consumption who fulfill the inclusion and exclusion criteria, getting admitted at VIMSAR, Burla during the period of December 2019 to December 2021.

Method of collection of specimens and processing:

Inclusion criteria:

1. All symptomatic patients who had ingested organophosphorus compound.

Exclusion criteria:

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1. Patients who had ingested other substance in addition to OP were excluded.
2. Patients having pre-existing heart disease like Rheumatic heart disease, Ischemic heart disease, Hypertensives, CKD, Chronic Alcoholics.

Patients were classified into three grades using 'Peradeniya organophosphorus poisoning scale' (POP). Changes in ECG were monitored and serum CPK–MB and Trop-I levels were measured at admission, repeated after 3 days and at discharge. Trop-I levels ≥0.04 mg/ml and CPK – MB levels >16 IU/L were considered as significant. Trop-I levels were estimated by ELISA and CPK-MB were measured using IFCC method.

The purpose of the study were explained to the patients and informed consent obtained. For all the patients, Glasgow coma scale (GCS), poisoning severity scale (PSS), and Peradeniya Organophosphorus poisoning (POP) score were assessed at the time of admission. Relevant blood test i.e Serum acetyl cholinesterase, S.CPK-MB, S.Trop-I, Blood Urea, S. Creatinine, ECG, CBC, RBS, Serum Electrolytes, Urine Routine were done.

RESULT

A total of 97 patients with OP poisoning admitted to medicine ward of VIMSAR, Burla from Dec2019 to Dec2021, over a period of 2 years. The age of the patients were from 45 to 60 years with the mean of 41.02 $\pm$ 14.64. The most common compound consumed was Chlorpyriphos (23.7%) followed by Phorate (22.7%). In 15.5% of the patients the compound remained unknown [Table-**I**]. The most common clinical finding in patients was Bradycardia (49.5%) followed by Tachycardia (49.5%). Hypotension was seen in 26 (26.8%) patients and 11 (11.3%) showed hypertension **[Fig-I**]. 73 (75.3%) of the patient had a significantly lower levels of serum Acetylcholinesterase level <2500 IU/L [**Table-II**].

TABLE I: OP COMPOUND CONSUMED BY THE PARTICIPANTS

TYPES OF OP COMPOUND	NUMBER	PERCENTAGE
Chlorpyriphos	23	23.7
Phorate	22	22.7
Dimethoate	16	16.5
Methyl parathion	12	12.4
Quinalphos	9	9.3
Unknown	15	15.5

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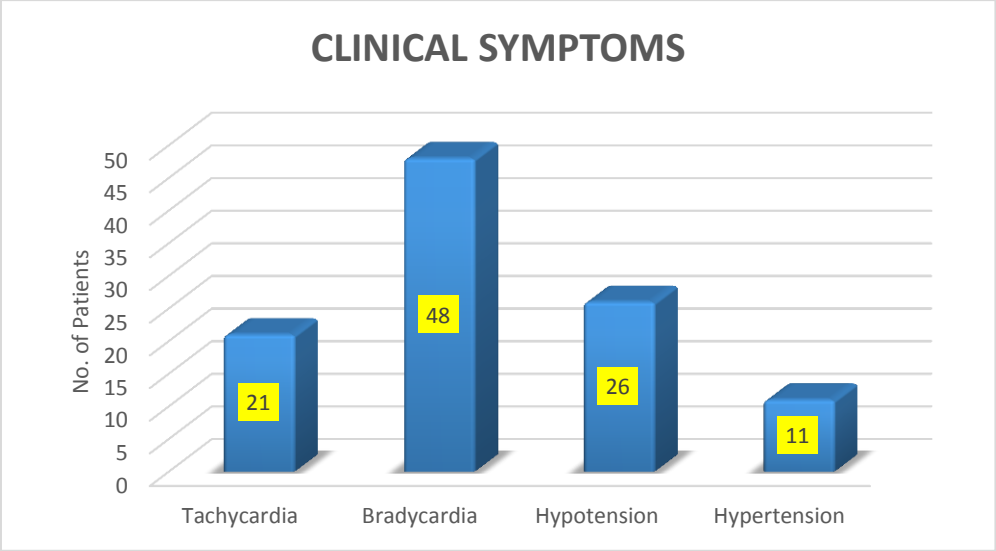
TABLE II: CHOLINE-ESTARASE LEVEL AMONG THE STUDY PARTICIPANTS

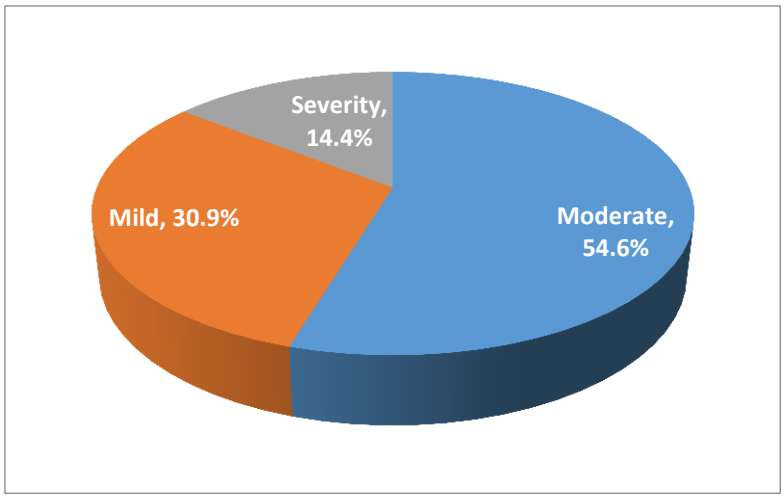
ACETYLCHOLINESTERASE LEVELS (U/L)	NUMBER	PERCENTAGE
<2500	73	75.3
>2500	24	24.7

FIGURE-I : Clinical Symptoms of the Study Participants



Majority of the patients had a moderate (54.6%) to mild (30.9%) severity of organophosphorus poisoning at presentation and (14.4%) having severe poisoning. (Fig.II)

FIGURE-II : PREVALENCE OF SEVERITY AMONG THE STUDY PARTICIPANTS TO THEIR PERADENIYA SCORE



In this study, ECG finding in decreasing order, Sinus bradycardia 43 (44.3%), QT Prolongation 33 (34.0%) followed by Sinus tachycardia 25 (25.8%) and ST Elevation 12 (12.4%) [**Fig. –III**]. Raised cardiac markers were found significant on day-3 [**Fig. –IV & V**]

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FIGURE III : ECG Finding among the Study Participants

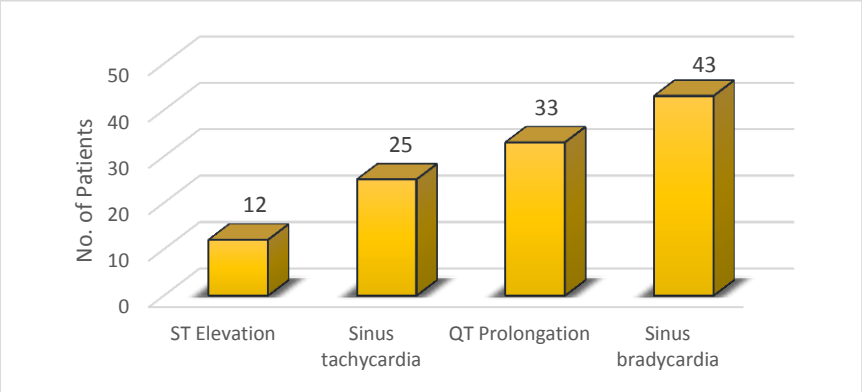

FIGURE IV : Distribution of Patients According To Trop –I Values

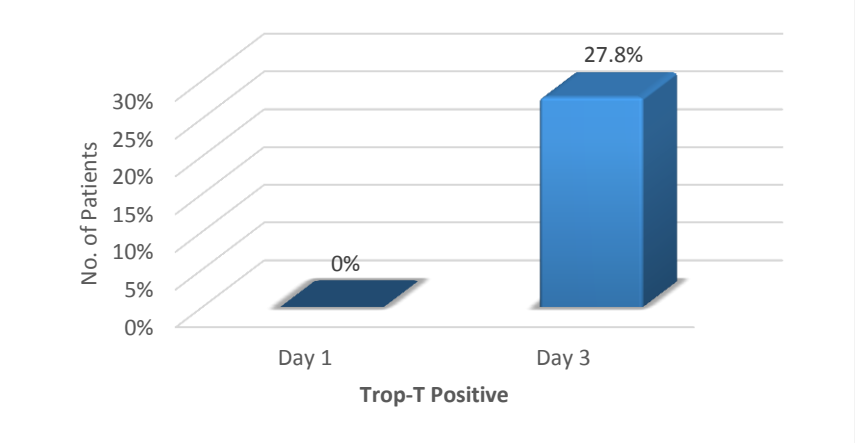

FIGURE V : Distribution of Patients According To CPK-MB

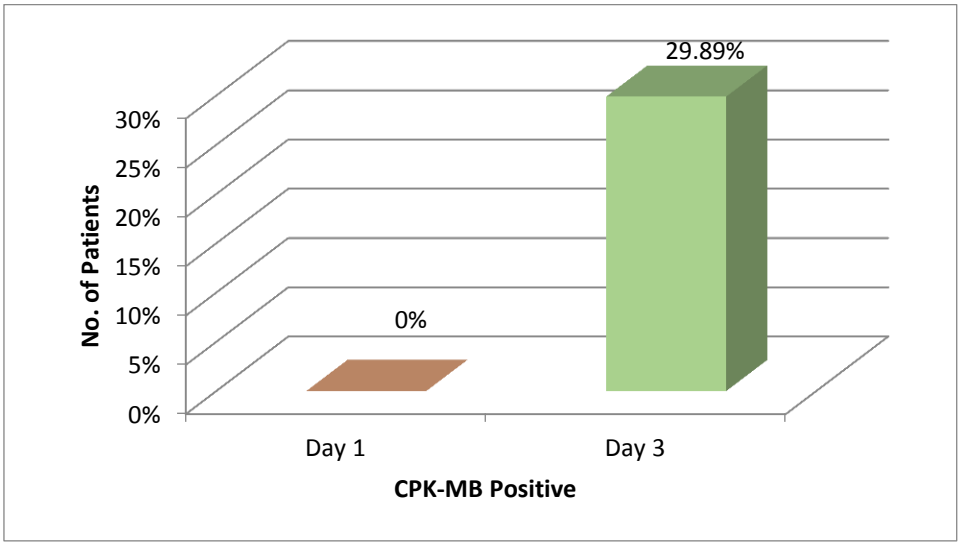

Table –III shows the proportion of patients with respiratory failures. In the current study there were 10 deaths (10.3%) and 39 (40.2%) went into respiratory failure who required mechanical ventilation. (Table-IV)

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TABLE III: PROPORTION OF PATIENTS WITH RESPIRATORY FAILURE

RESPIRATORY FAILURE	NUMBER	PERCENTAGE
Absent	58	59.8
Present	39	40.2

TABLE IV: PREVALENCE OF DEATH AMONG THE STUDY PARTICIPANTS

OUTCOME	NUMBER	PERCENTAGE
Death	10	10.3
Discharge	87	89.7

Table V shows out of 29 patients with significantly raised CPK-MB at day 3, 25 out of 39 patients (64.10%) with positive CPK-MB and 14 of 39 patients (35.9%) with negative CPK-MB developed respiratory failure. 25 of 39 (64.10%) patients with QT prolongation on ECG, and 14 of 39 (35.9%) patients without QT prolongation also developed respiratory failure. out of 27 patients with elevated Trop-I at day 3, 21 (53.90%) of 39 and 18(46.10%) of 39 with negative Trop-I developed respiratory failure.

TABLE V: ASSOCIATION BETWEEN CARDIAC MARKER AND RESPIRATORY OUTCOME

	No Respiratory Failure (n=58)	Respiratory Failure (n=39)	P Value
CK-MB at day 3			
Negative	54(93.1%)	14 (35.9%)	**<0.001**
Positive	4 (6.9%)	25 (64.1%)	
Trop – I at day 3			
Negative	52 (89.6%)	18 (46.1%)	**<0.001**
Positive	6 (10.4%)	21 (53.9%)	
ST. Elevation			
Absent	56 (96.6%)	29 (74.4%)	**<0.001**
Present	2 (3.4%)	10 (25.6%)	
QT. Prolongation			
Absent	50 (86.2%)	14 (35.9%)	**<0.001**
Present	8 (13.8%)	25 (64.1%)	

Table VI shows 0 of 30 (0%) mild patient, 6 out of 53 (11.30%) moderate patient and 6 out of 14 (42.90%) severe patient associated with ST elevation. So ST elevation mostly

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predominate in patients with severe poisoning. Q-T prolongation was seen only 3 (10%) in mild, 21 (39.6%) in moderate poisoning and 9 (64.3%) patient with severe poisoning (p value <0.001) so statistically significant relationship found between Q-T prolongation and clinical severity of patient. Cardiac enzyme raised 0 out of 30 (0%) patient in mild, 18 of 53 (34.00%) in moderate and 9 of 14 (64.30%) in severe poisoning. Hence elevated cardiac enzyme most commonly seen in severe poisoning with p value <0.001, so the relationship found statistically significant. Raised CPK-MB was seen 0 (0%) in mild cases, 21 (39.6%) in moderate cases and 8 (57.1%) in severe cases. The study is clinically significant because p value <0.001.

TABLE VI: ASSOCIATION OF CARDIAC MARKERS WITH CLINICAL SEVERITY

	Mild (n=30)	**Moderate (n=53)**	**Severe (n=14)**	**Total (n=97)**	**P Value**
ST. Elevation					
Absent	30 (100%)	47 (88.7%	8 (57.1%)	85 (87.6%)	**<0.001**
Present	0 (0.0%)	6 (11.3%)	6 (42.9%)	12 (12.4%)	
QT. Prolongation					
Absent	27 (90.0%)	32 (60.4%)	5 (35.7%)	64 (66.0%)	**<0.001**
Present	3 (10.0%)	21 (39.6%)	9 (64.3%)	33 (34.0%)	
Trop –I day 3					
Negative	30 (100%)	35 (66.0%)	5 (35.7%)	70 (72.2%)	**<0.001**
Positive	0 (0.0%)	18 (34.0%)	9 (64.3%)	68(70.1%)	
CPK-MB day 3					
Negative	30 (100%)	32 (60.40%)	6 (42.9%)	32 (52.5%)	**<0.001**
Positive	0 (0.0%)	21 (39.6%)	8(57.1%)	29 (29.9%)	

In this study the mean Trop- I and CPK –MB levels in patients with respiratory failure was 0.49 ± 0.26 mg/ml and 38.33 ± 30.50 IU/L which were higher than the level seen in normal patient 0.22 ± 0.17 mg/ml and 12.55±6.47 respectively **[Table-VII]**. The mean (SD) of Trop-I and CPK-MB levels in patients with Serum cholinesterase levels were 0.38 ± 0.26 IU/L and 2765 ± 26.64IU/L, which were higher than the level in normal patients 0.13 ± 0.09 and 11.22 ± 3.42. P. Value (<0.001) [Table-**VIII**].

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Table VII : ASSOCIATION OF RESPIRATORY FAILURE WITH MEAN VALUES OF CARDIAC MARKERS

	Absent (N=58)	**Present (N=39)**	**P Value**
Trop_1_3			
Mean (SD)	0.22 (0.17)	0.49 (0.26)	**<0.001**
Range	0.01-0.70	0.10-1.10	
CPK_MB_3			
Mean (SD)	12.55 (6.47)	38.33 (30.55)	**<0.001**
Range	6.00-42.00	7.00-132.00	

Table VIII : ASSOCIATION OF SERUM CHOLENESTRASE LEVELS WITH MEAN VALUES OF CARDIAC MARKERS

	<2500 (N=73)	**>2500 (N=24)**	**P Value**
Trop_1_3			
Mean (SD)	0.38 (0.26)	0.13 (0.09)	**<0.001**
Range	0.10 – 1.10	0.01 – 0.40	
CPK_MB_3			
Mean (SD)	27.65 (26.64)	11.22 (3.42)	**<0.001**
Range	6.00-132.00	6.00-15.00	

DISCUSSION:

In this study 97 patients of organophosphorus poisoning taken, who were admitted to VSSIMSAR, Burla with varying degree of severity. The highest number of patients were in the age group 45- 60 years (26.8%), followed by 35-45 years (23.7%) and 25- 35 years (19.56%). The incidence of poisoning was more in males (58.8%) as compared to females (41.2%). This study is well correlated with study done by Dash et al.[6], which showed an incidence of 67% in males and 23% in females.

Organophosphorus compound:

Chlorpyriphos (23.7%) was the most common compound implicated in the poisoning. It was followed by Phorate (22.7%), Dimethoate (16.5%) and Methyl parathion (12.4%). This was different from the study done by P Karki et al.[7], who found the most common compound as Methyl parathion (23%) followed by Propoxur (5%), which can be explained by the difference in availability of compound in a particular geographic location. In 15

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patients (15.5%) the compound was not brought and the patient was diagnosed and treated on the basis of clinical features. Among the 29 patients who were found to have raised cardiac enzymes, Chlorpyrifos was the compound in 16 patients, Methyl parathion in 9 patient, Dimethoate in 3 patients and Quinalphos in 1 patient. Statistically significant relationship could be established between the compound consumed and the cardiac involvement.

Severity of poisoning:

Peradeniya organophosphorus poisoning (POP) scale:

The Peradeniya Organophosphorus Poisoning (POP) Scale is a scoring system introduced by N Senanayake, H J de Silva and L Karalliedde in 1993. Common clinical manifestations of OP poisoning are selected as parameters and each is assessed on a three-point scale varying from 0 to 2 (Table 4). A score of 0 to 3 is considered as mild poisoning, 4 to 7 as moderate poisoning and 8 to 11 as severe poisoning.

Table IX Peradeniya organophosphorus poisoning scale [19]

Parameters	Criteria	Score
Pupil Size	≥ 2mm < 2 mm Pinpoint	0 1 2
Respiratory rate	< 20/min ≥ 20/min ≥20/min with central cyanosis	0 1 2
Heart rate	> 60/min 41-60/min <40/min	0 1 2
Fasciculation	None Present, generalized/continuous Both generalized and continuous	0 1 2
Level of Consciousness	Conscious and rationale Impaired response to verbal commands No response to verbal commands	0 1 2
Seizures	Absent	0

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	Present	1
Note: 0-3-mild poisoining, 4-7-Moderate poisoining, 8-11- severe poising		

Out of the 97 patients 30 (30.9%) had mild, 53 (54.6%) had moderate and 14(14.4) had severe level of poisoning. [Fig.1]. Similar findings was presented in the study done by Pradeep et al.(19) There was not much variation in distribution of severity between males and females. The severity correlated with reduction of plasma cholinesterase level, which showed a mean cholinesterase levels of 2679.12 IU/L (± 950.13) in mild, 2251.09 IU/L (±1178) in moderate and 1162 IU/L (±801) in severe. These values agreed with the study done by Kuntal Bhattacharyya et al.[8] which showed a similar amount of plasma cholinesterase reduction with increasing severity.

Clinical features (Cardiovascular):

Bradycardia 48 (49.5%) was the most common clinical sign seen in the present study at the time of admission. Tachycardia was seen in 21 (21.6%) patients, explained by the Inj. Atropine given to these patients at the primary health care level. Blood Pressure changes in the form of hypertension (systolic BP ≥140 and/or diastolic BP ≥90 mm Hg) and hypotension (Systolic BP ≤ 90 mm Hg) were seen in 11 (11.3%) and 26 (26.6%) patients respectively. Saadeh AM et al.(9) concluded that hypertension is more common [**TABLE X]**, whereas Mathur et al.(15) reported that hypotension is more common than hypertension, but there is a chance of getting both in case of OPC poisoning.

TABLE X: Comparison of clinical features with other studies

Clinical signs	A.M. Saadeh et al.[9]	Present study
Tachycardia	35%	21%
Bradycardia	28%	49%
Hypertension	22%	11%
Hypotension	17%	26%

In the current study abnormal ECG was found in 62 cases as evidenced by Sinus bradycardia 43 (44.3%), QT prolongation (Q-Tc ≥ 0.42 secs in males and ≥0.43 secs in females) in 33(34.02%) patients. ST elevation (≥2 mm above the isoelectric line), which was found in 12 patients (12.37%) and sinus tachycardia in 25(25.77) patients. This differed from the other studies.

In the study done by Balouch et al[10] and Saadeh et al.[9] Q-T prolongation was the most common ECG abnormality, as compared Sinus bradycardia being the most common

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finding in this study. Q-T prolongation was seen only in 34.02% of the patients in this study as compared to 67% in study by Saadeh et al. ST segment elevation was seen 12.37 % of the patients, which was similar to the study by Balouch et al. (10.3%). According to Manoharan. S. et al.[11] 75% of the study population had prolonged QTc. [**TABLE XI**]

TABLE XI :Comparison of ECG changes with other studies

ECG changes	Balouch et al[10]	Saadeh et al[9]	Present study
ST elevation	10.3%	24%	12.37
Q-T prolongation	17.2%	67%	34.02%
Sinus tachycardia	12.6%	35%	25.77%
Sinus bradycardia	14.9%	28%	44.3%

Q-T prolongation was seen in 3 (10 %) patients with mild poisoning, 21 (39.6 %) patients with moderate poisoning and 9 (64.33%) patients with severe poisoning (P value 0.001) indicating that prolonged Q-T interval may be an indicator of severity. So statistically significant relationship found between Q-T prolongation and clinical severity of the patients (p value< 0.001). Q-T interval prolongation was associated with 25 of 39 (64 %) patients who developed respiratory failure and needed mechanical ventilator as compared to 14 of 39 patients (35.9 %) without Q-T interval prolongation also developed respiratory failure (p value <0.0001).

Patients with POP scale of moderate and severe poisoning developed acute respiratory failure was also found by Anjana. D.[16] Banday. TH. et al[20] & Gyanwani. P.R. et al.[21] So statistically significant relationship found between Q-T prolongation and respiratory failure of the patient (p value< 0.001).

Markers of myocardial injury:

In the present study cardiac enzymes (Trop-I and CPK-MB) are used as an indicator of cardiac injury (Troponin I >0.4 mg/ml and CPK-MB ≥16 U/L). Out of 97 OPC poisoning patients 27(27.8%) and 29 (47.5%) had elevated Troponin-I and CPK –MB respectively on day 3 of admission. All the patients who showed enzyme positivity also had ST segment elevation on ECG, both of which reverted back at the time of discharge suggesting a transient ischemic process as described by Kiss and Fazekas.[17] Out of 29 patients with elevated CPK

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MB on day 3, 25(64.1%) patients developed respiratory failure, and 14 out of 39 patients (35.9%) with normal CPK MB also developed respiratory failure (p value 0.011).

Out of 27 patients with elevated Trop-I on Day 3, 21 (53.9%) patients developed respiratory failure and out of 39, 18 (46.1%) patients with normal Trop-I also developed respiratory failure, which is indicating that patients with raised cardiac enzymes have higher chance of developing respiratory failure.

Cardiac enzymes were raised 0 out of 30 (0.%) patients in mild, 18 of 53 (34%) patients in moderate and 9 of 14(81.8%) patients in severe poisoning. Hence raised cardiac enzymes were most commonly seen in severe poisoning, with this study p value is < 0.001. So this relationship was statistically significant. Out of the 29 patients who had raised cardiac enzymes, 10 died. This was also found have statistical significant (p value 0.001). The mean Trop-I levels in mild, moderate and severe group were 0.13 ± 0.07, 0.37 ± 0.24 and 0.60 ± 0.23 mg/ml respectively. Similarly the CPK-MB levels were 11.06 ± 3.19, 24.97 ± 20.37 and 51.44 ± 40.95 I U/L in mild moderate and severe cases respectively. As it can be seen that Trop-I and CK-MB showed increased levels with increasing severity of poisoning in Dr. Hasan K.K. et al. study.[18] This trend was also seen in the study conducted by Wang Jian-Dong et al. **[TABLE XII]**

TABLE XII : Comparison of CK-MB levels changes with other studies

	Wang Jian-Dong et al.[5] (U/L)	**Present study (IU/L)**
Mild	37.1 ± 5.6	24.04 ± 7.86
Moderate	68.3 ± 9.71	24.97 ± 20.37
Severe	112.4 ± 12.5	38.88 ± 40.95

The mean Troponin I and CK-MB value also showed a higher value in patients who died when compared to patients who survived. The mean value in patient who died Trop- I was 0.56± 0.29 mg/ml and CK-MB was 61.60 ± 42.42 I U/L which was higher than the levels seen in survivors (Trop- I-0.32± 0.24 mg/ml and CK-M 21.98 ± 20.87 I U/L). The higher values were found 141.50 ± 13.43 ng/ml in dead patients compared to 15.06 ± 19.21 ng/ml in discharged patients as found in study done by Sharma R et. al.[12] Thus the higher Trop- I and CK-MB values were associated with a higher incidence of mortality and respiratory failure, hence suggesting its use as a prognostic indicator. Similar finding was found by the study done by Patil et al. [13] Elevation of Trop I within 48 hours was seen in 34 patients

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(34.3%) as found in Cha. Y.S. Study [14]. It was also seen that, in patients who developed respiratory failure, higher titers of cardiac enzyme was associated with increased duration of ICU stay. In this study the mean Trop- I and CPK-MB levels in patients was 0.49± 0.26 mg/ml and 38.33± 30.50 IU/L respectively.

CONCLUSION:

Majority of the patients were in the age group of 45- 60 years. The older age group were most susceptible for severe degree poisoning. Males were more than females in the study but severity was similar in males and females.

The occurrence of cardiotoxicity was found to be related to the type of compound used for poisoning.

The most common clinical sign related to cardiovascular system was bradycardia followed by hypotension which was associated with severe degree of poisoning.

Most common ECG finding was bradycardia followed by Q-T prolongation. Prolonged QT interval was found to be indicator of severity and also had a prognostic value in predicting death and respiratory failure. The positivity of cardiac enzymes was found in moderate to severe poisoning. Patients with elevated cardiac enzymes developed respiratory failure and death.

The level of cardiac enzymes correlated well with the severity of poisoning, prolonged ICU stay and outcome, suggesting its use as a prognostic indicator in organophosphorus poisoning.

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