EVALUATION OF THE POTENTIAL CARDIOTOXICITY IN ACUTELY INTOXICATED ORGANOPHOSPHATE CASES

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Article History: Received: 15.05.2023 **Revised:** 25.06.2023 **Accepted:** 01.07.2023

Abstract

Background: Poisoning with organophosphorus compounds is responsible for great morbidity and mortality all over the world especially in developing countries including Egypt**.**

Aim: This study aimed to determine the cardiotoxic effects and ECG changes in acutely intoxicated organophosphorus poisoning cases in order to understand its prognostic significance and to reduce morbidity, mortality and hospital stay by its early detection and management.

Subject and Methods: This was a prospective cross-sectional observational study. It was performed in the period from the 1st of September 2020 to 28th of February 2021. It has been designed to determine the potential cardiotoxicity and electrocardiographical manifestations of acutely intoxicated organophosphate patients presented at the Emergency Unit of Assiut University Hospital.

Results: QT interval and QTc duration were significantly increased with mortality where they were longer in died than discharged patients (288.67 ± 51.38 vs 352.43 ± 57.47, P=0.007, and 398.49 ± 57.25 vs 527.71 ± 106.05, P=0.002) in recovered and died patients respectively.

Conclusion: Acute organophosphorus poisoning can be associated with severe cardiac complications within few hours of exposure. ECG grading is a predictor for both primary and major adverse outcome of patients with acute organophosphorus poisoning. The corrected QT interval could be considered as an excellent parameter to predict morbidity and mortality in patients with acute organophosphorus poisoning and it was an alarming sign of major outcome in patients with acute organophosphorus poisoning. Serum cardiac Tn-I level could be considered an effective predictor of direct myocardial toxic effect induced by organophosphorus compounds. Moreover, the ability of severe organophosphorus poisoning to cause direct myocardial injury apart from rhythm disturbances was assured.

Keywords: Cardiotoxicity; Organophosphate cases; myocardial toxic; organophosphorus poisoning.

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DOI: 10.48047/ecb/2023.12.10.1016

Introduction

A majority of the pesticide poisonings in developing countries is caused by organophosphates (OP). These cholinesterase inhibiting pesticides are also a public health problem in some industrialized countries.

Poisoning with OP compounds is responsible for great morbidity and mortality all over the world especially in developing countries including Egypt. OP Poisoning among all poisoning cases is nearly 46.1%, with a mortality rate of 2.7%. Among OP poisoning cases, the case fatality rate varies from 10 to 30% mainly in developing countries including Egypt [(1)]**.**

The toxic effects of these compounds are the consequence of the inhibition of acetylcholinesterase enzyme (AchE) in the nervous system, leading to accumulation of the neurotransmitter acetylcholine at synapses and myoneural junctions resulting in the continued over stimulation of acetylcholine receptors [(2)]**.** The severity of OP poisoning differs according to the nature of the compound, its quantity, the way through which the exposure has occurred and the delay time of initiating the treatment [(3)].

Cardiac manifestations may range from minor ECG manifestation such as sinus tachycardia to life threatening complications including cardiogenic pulmonary edema. Repolarization abnormalities including ST segment elevation and T wave inversion as well as prolongation of QTc interval are the most frequent cardiac manifestations of acute organophosphate poisoning [(4)].

Cardiac complications often accompany poisoning with these compounds, particularly during the first few hours. These complications are potentially preventable, if they are recognized early and treated adequately. The extent, frequency, and pathogenesis of the cardiac toxicity from these compounds have not been clearly defined [(5)]**.**

There are emerging options for new cheap and/or easily quantifiable biochemical markers like troponin I (cTnI), creatine phosphokinase (CPK) and C-reactive protein (CRP) that facilitate the prediction of the severity and/ or the outcome of cardiotoxicity by these compounds [3, 6].

This study aimed to determine the cardiotoxic effects and ECG changes in acutely intoxicated organophosphate poisoning cases in order to understand its prognostic significance and to reduce morbidity, mortality and hospital stay by its early detection and management.

Patients and Methods

This was a prospective cross-sectional observational study. The duration of the study was six month from the 1st of September 2020 to 28th of February 2021. It has been designed to determine the potential cardiotoxicity and electrocardiographical manifestations of acutely intoxicated organophosphate patients presented at the Emergency Unit of Assiut University Hospital.

Inclusion Criteria: Acutely intoxicated organophosphate patients presented at Emergency Unit of Assiut University Hospital during the period from 1st of September 2020 to the 28th of February 2021.

Exclusion Criteria: 1- Patients with history of cardiac diseases, patients exposed to other cardiotoxic substances, patients on anticholinergic therapy, patients on medications that may cause ECG abnormalities or affect QT interval as Antipsychotics and Class IA, IC antidysrrhythmics, patients with physiological or pathological conditions that affect cholinesterase level like pregnancy and myasthenia gravis respectively and patients younger than 18 years old.

Methods: Full detailed history was obtained (either from the patient after stabilization of his or her condition if the patient was conscious or from the relatives in case of comatose patient).

Ethical approval: An informed written consent was taken from the patients themselves or from the parents if the patient cannot give consent for inclusion in the study for obtaining medical history, clinical examination, ECG and for the permission to take blood samples for laboratory investigations. The confidentiality of all data in this study was protected to the fullest extent possible. All ethical aspects related to research in Assiut University were implicated in this study after the approval of the ethical committee under No.17101295.

The following data was collected for every patient included in our study:

Demographic data: Gender (male or female), age, marital status (single, engaged, married or divorced), occupation (employed or not), socioeconomic state, special habits (smoking, alcohol or drug abuse), history of psychiatric illness and history of chronic diseases (diabetes mellitus, hypertension, asthma, cancers, thyroid diseases or epilepsy, etc.).

History related to the poisoned substance: Dose, type of the substance used, route of exposure (through skin, by inhalation or by ingestion), time of poisoning, manner of exposure (suicidal, homicidal or accidental), first aid measures and time of arrival.

History of presenting symptoms of intoxication:

Complete clinical examination: General Examination including: Assessment of conscious level by Glasgow coma scale, assessment of vital signs: (Pulse, blood pressure, respiratory rate and temperature) and pupil examination. **Systemic Examination including:** Cardiac examination, respiratory examination, abdominal examination and neurological examination

Investigations: An arterial blood sample and a venous blood sample were taken from all patients for: complete blood count (CBC) and arterial blood gas (ABG) analysis as the pH is an important prognostic factor and the HCo_3level to determine the need for Hco_3 infusion or not in the treatment. The recorded parameters include: PH (Power of Hydrogen), Pco_2 (carbon dioxide partial pressure), Hco_3 (bicarbonate level) and lactic acid. Other investigations include hepatic function tests (Liver enzymes, serum albumin & prothrombin concentration), renal functions tests (blood urea & serum creatinine). Electrocardiography is a main investigation for patients in our study. It was done for every patient on admission and repeated according to the progression of the patient status. Cardiac biomarkers (Troponin, CPK & CRP) were also done for all cases.

Outcome of the case: Each patient was followed up until: Complete recovery**,** complications (arrhythmia, pneumonia, intermediate syndrome & others) and death

Statistical Analysis: All statistical calculations were done using SPSS (statistical package for the social science; SPSS Inc., Chicago, IL, USA) version 22. Data were statistically described in terms of mean ± standard deviation (±SD), or median and range when not normally distributed, frequencies (number of cases) and relative frequencies (percentages) when appropriate. Mann-Whitney U test was used for comparing non-normally distributed quantitative data. For comparing categorical data, Chi square ($\chi 2$) test was performed. Fisher Exact test was used instead when the expected frequency is less than 5. Odds ratio (OR) with 95% Confidence Interval (CI) and Logistic Regression was calculated to measure the different risk factors for mortality. P-value is always 2 tailed set significant at 0.05 level.

Results

This study was conducted at Emergency Unit of Assiut University Hospital. It is a prospective cross-

sectional observational study. It was performed in the period of six months from the 1st of September 2020 to 28 th of February 2021. It has been designed to determine the potential cardiotoxicity and electrocardiographical manifestations of acutely intoxicated organophosphate patients.

Table 1 shows that the total number of the studied cases was 80. It shows that the mean age of the studied cases was 30.09 ± 11.37 years and ranged from 17 to 55 years. Most of patients were belonging to the age group (<18 – 40 years) representing 78.75% of the patients in the study, while 21.25% of patients were in the age group > 40 -60 years.

Table (1): Socio-demographic characteristics of the studied participants (n=80)

Variable name	N	(%)
Age groups (years)		
• <18 – 40	63	(78.75)
• >40 – 60	17	(21.25)
• Mean ± SD	30.09 ± 11.37	
• Median (range)	27 (17 – 55)	
Sex		
• Male	32	(40)
• Female	48	(60)
Working status		
• Worker	39	(48.75)
• Not worker	30	(37.5)
• Student	11	(13.75)
Socioeconomic status		
• Married	47	(58.75)
• Single	31	(38.75)
• Engaged	2	(2.5)
Special habits	27	(33.75)
Type of special habit		
• Cigarette smokers	24	(88.9)
• Cigarette smoker and cannabis addict	1	(3.7)
• Cigarette smoker and opiate addict	1	(3.7)
• Cigarette Smoker and tramadol addict	1	(3.7)

Quantitative data are presented as mean ± SD and median (range), qualitative data are presented as number (percentage).

Table 2 reveal the data related to OP exposure as regarding the route of intake; most of studied cases were exposed to the OP compounds through oral route by ingestion (86.25%), and (13.75%) through inhalation. As regarding manner of poisoning, 67.5% of patients were intoxicated due to suicidal attempt, while accidental exposure occurred in 32.5% of patients.

Table (2): Route of intake, manner of poisoning, dose, and type of the exposed compound among the studied patients (n=80)

Variable name	N	(%)
Route of exposure		
• Oral	69	(86.25)
• Inhalation	11	(13.75)
Manner of poisoning		
• Suicidal	54	(67.5)
• Accidental	26	(32.5)
Dose		
• Known dose	60	(75)
• Unknown dose	20	(25)
Type of compound		
• Unknown	67	(83.75)
• Toxefen	7	(8.75)
• Malathion	6	(7.5)

Quantitative data are presented as median (range), qualitative data are presented as number (percentage).

Fig.1 show that there was high significant relation between the outcome and blood pressure, heart rate and respiratory rate, where hypotension and tachycardia were recorded more in died patients than recovered cases (P=0.000, and 0.033) respectively, and also bradypnea was more in died patients (P=0.013).

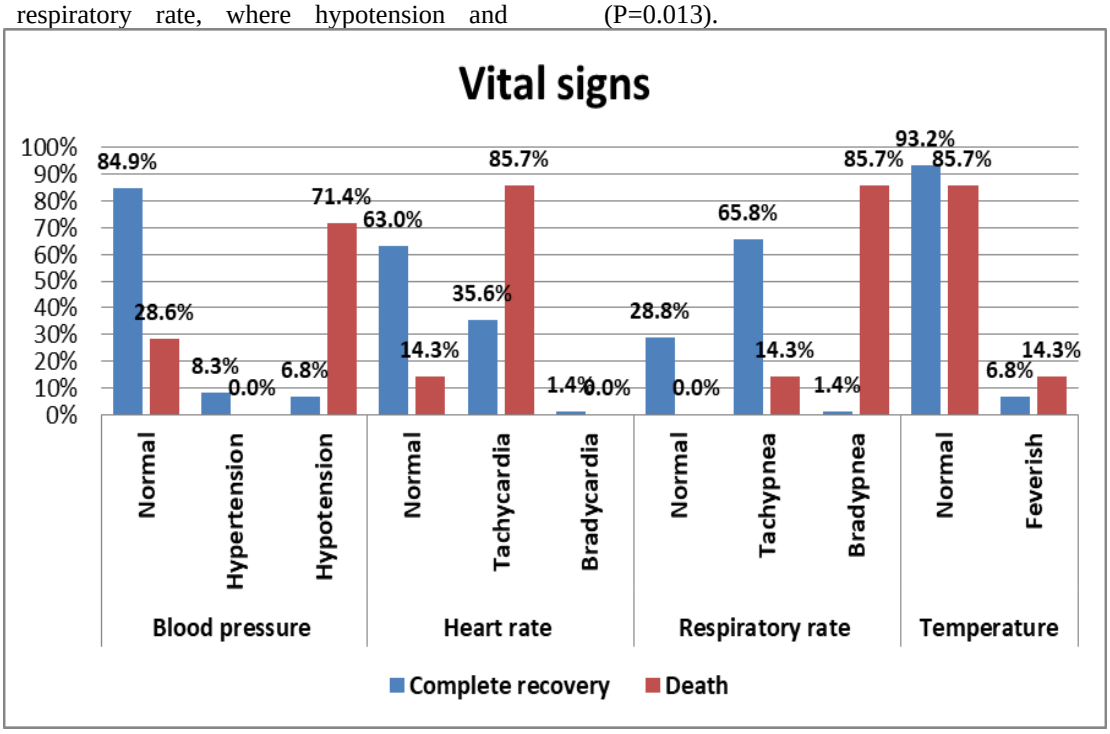

Fig. (1): Bar graph showing the distribution of vital signs among patients with complete recovery and died cases

Table 3 shows that QT interval and QTc duration were significantly increased with mortality where they were longer in died than discharged patients (288.67 ± 51.38 vs 352.43 ± 57.47, P=0.007, and 398.49 ± 57.25 vs 527.71 ± 106.05, P=0.002) in recovered and died patients respectively.

Table (3): Relations between ECG abnormalities of the studied participants and their outcome "died and recovered" (n=80)

Variable name	Complete recovery (n=73)	Death (n=7)	P value
Heart rate (beats/minute)			0.310*
• Mean ± SD	98.03 ± 24.95	109.86 ± 24.53	
• Median (range)	88 (55 – 150)	116 (56 – 128)	
QT (msec)			**0.007***
• Mean ± SD	288.67 ± 51.38	352.43 ± 57.47	
• Median (range)	264 (225 – 456)	377 (258 – 420)	
QTc (msec)			**0.002***
• Mean ± SD	398.49 ± 57.25	527.71 ± 106.05	
• Median (range)	389 (294 – 499)	533 (322 – 630)	

Quantitative data are presented as median (range). Significance defined by $p < 0.05$.
*Mann-Whitney U test was used to compare the mean differences between groups

Table 4 shows that there was significant association between development of sinus tachycardia, and prolonged QTc and the outcome of the studied cases where these arrhythmias were more among died than recovered patients (P=0.010, and 0.028) respectively.

Table (4): Relations between arrhythmias developed among the studied participants and the outcome "died and discharged" (n=80)

Arrhythmias developed	Complete recovery (n=73)		Death (n=7)		P value
• Sinus tachycardia	24	(32.9)	6	(85.7)	**0.010****
• Sinus bradycardia	2	(2.7)	1	(14.3)	0.243**
• Prolonged QTc	6	(8.2)	3	(42.9)	**0.028****

Qualitative data are presented as number (percentage). Significance defined by $p < 0.05$.
**Fisher's Exact test was used to compare the frequency differences between groups

Table 5 reveals that there was high statistically significant increase in the mean of CRP, and cardiac enzymes (Troponin and CPK) levels in died patients as compared to recovered ones (P<0.001, for all).

Table (5): Cardiac Biomarkers **(**CRP, Troponin, and CPK) in the studied patients "died and recocered" (n=80)

Cardiac biomarkers	Complete recovery (n=73)		Death (n=7)		P value
CRP (mg/L)					
• Normal	42	(57.5)	0	(0.0)	**0.004****
• Raised	31	(42.5)	7	(100.0)	**0.000***
• Median (range)	6 (1 – 351)		250 (187 – 1258)		
Troponin (migram/L)					
• Normal	57	(78.1)	0	(0.0)	**0.002****
• Raised	16	(21.9)	7	(100.0)	**0.000***
• Median (range)	0.02 (0.0 – 0.9)		0.17 (0.07 – 0.8)		
CPK (U/L)					
• Normal	56	(76.7)	0	(0.0)	**0.000****
• Raised	17	(23.3)	7	(100.0)	**0.000***
• Median (range)	162 (44 – 478)		352 (252 – 565)		

Qualitative data are presented as number (percentage). Significance defined by $p < 0.05$.
*Mann-Whitney U test was used to compare the mean differences between groups
**Fisher's Exact test was used to compare the frequency differences between groups

Table 6 show that 91.25% of the studied cases were recovered and returned to home, versus seven cases (8.75%) who died; four cases were died due to cardiac arrest, and three cases were died by pneumonia.

Table (6): Outcome of the studied cases and cause of death (n=80)

Variable name	N	(%)
Outcome		
• Survived	73	(91.25)
• Died	7	(8.75)
Cause of death		
• Cardiac arrest	4	(57.1)
• Pneumonia	3	(42.9)

Qualitative data are presented as number (percentage).

Table 7 reveals by using the multivariate logistic regression "Backward regression" analysis that only older age and raised liver functions as significant predictors of mortality among the studied cases (OR=38.836, 95%CI= 2.381 - 633.335, P= 0.010, and OR=18.220, 95%CI= 1.318 - 251.816, P= 0.030) respectively

Table (7): Logistic regression analysis for prediction of mortality among the studied cases

Variables	N	Univariate analysis			Multivariate analysis		
		OR	P value	95% CI	OR	P value	95% CI
Age (years)							
< 18 – 40	63	ref			ref		
> 40 – 60	17	12.708	**0.004***	2.202-73.332	38.836	**0.010***	2.381-633.335
Dose (cc)	80	1.025	**0.002***	1.009-1.041	Not included in the model		
Blood pressure							
Normal	64	ref			ref		
Abnormal	16	14.091	**0.003***	2.422-81.963	4.319	0.222	0.413-45.148
Heart rate							
Normal	47	ref			0.000	0.999	0.0-NA
Abnormal	33	10.222	**0.036***	1.168-89.50			
Respiratory rate							
Normal	52	ref			ref		
Abnormal	28	13.909	**0.018***	1.580-122.459	15.407	0.052	0.980-242.259
QT	80	1.018	**0.009***	1.005-1.032	Not included in the model		
QTc	80	1.030	**0.003***	1.010-1.050	Not included in the model		
Sinus tachycardia							
No	50	ref			ref		
Yes	30	12.250	**0.024***	1.395-107.568	4.756	0.411	0.115-196.514
Cardiac enzyme					Not included in the model		
Normal	55	ref					
Raised	25	0.997	NS	0.00 - NA			
Liver function							
Normal	70	ref			ref		
Raised	10	14.889	**0.002***	2.682-82.665	18.220	**0.030***	1.318-251.816
Kidney function							
Normal	71	ref			ref		
Raised	9	18.133	**0.001***	3.148-104.444	1.572	0.726	0.126-19.641
Blood gases					Not included in the model		
Normal	49	ref					
Raised	31	0.997	NS	0.00 - NA			

OR= odds ratio, CI =confidence interval, NS=not significant, NA=not achieved, p value is significant ≤0.05
Odds ratio (OR) with 95% Confidence Interval (CI) and Logistic Regression was calculated to measure the different risk factors for mortality

Discussion

This study is an observational study including eighty acutely organophosphorus intoxicated patients admitted at the Emergency Department of Assiut University Hospital. They were selected according to predetermined criteria. Their demographic data, history, physical finding on admission, ECG, cardiac biomarkers, ABG, CBC, liver function tests, kidney function tests and outcomes for all patients were recorded.

In the present study the mean age for the patients was 30.09 ± 11.37 years and more than three quarters of them (78.75%) were between 18 and 40 years (teenager and middle age groups). This finding agreed with **Ahmed *et al.*** [7] **and Banday *et al.*** [8] in which the incidence was highest in patients aged less than 40 years. On the other hand, less than one quarter of patients (21.25%) were between the age of 40 years and the age of 60 years and this was in agreement with **Chintale *et al.*** [9]**.** This could be explained by the vulnerability to various emotional conflicts that can happen during this phase (teenager and middle age groups) of life in which the people are most ambitious, productive and responsible [8].

In the present study most of patients (86.25%) were exposed to the OP compounds through oral route, while only (13.75%) through inhalation.

This was in accordance with results of **Bilal *et al.*** [10]**; Çolak *et al.*** [11]**.**
Most of patients in the current study (67.5%) were intentionally exposed to OP while the remaining (32.5%) were intoxicated accidentally. These results agreed with **Ali *et al.*** [12]; **Hassan and Madboly,** [13] **and Banday et al.** [8] and many other studies.

In the current study, there was significant association between both the severity and occurrence of death and presentation with hypotension and tachycardia. This was in contrast to studies done by **Yun *et al,*** [14] **and Gunduz *et al.*** [15] in which there was no significant difference as regard systolic blood pressure between died and recovered cases.

Cardiac manifestations are commonly observed in patients with OP toxicity. These complications could be produced by different mechanisms [16]**.** Either by direct effect through increased sympathetic and/or parasympathetic activity or indirect through hypoxemia, acidosis and electrolyte imbalance [5]**.**

The mean heart rate of the patients in the present study was 99.06 ± 24.99 beats/min, and ranged from 55 up to 150 beats/min. The mean QT interval was 294.25 ± 54.64 msec, and ranged from 255 up to 456 msec and the mean QTc was 409.80 ± 72.05 msec, and ranged from 294 up to 630 msec. Fifty-nine percentage of patients did not develop arrhythmias while, (41.0%) developed arrhythmias in the form of sinus tachycardia in (37.5%), sinus bradycardia in (3.75%), and prolonged QTc interval in (11.25%).

In agreement with the current study **Karki *et al.*** [17] also reported that the most recorded ECG change was sinus tachycardia (40.5%) followed by prolonged QTc interval (37.8%), ventricular tachycardia (10.8%) then ventricular premature contractions (5.4%). In **Coskun *et al.*** [18] study the mean heart rate was 91±27 beat/minute and the most recorded type of arrhythmia was sinus tachycardia which agrees with finding in the present study.

In contrast to the present study **Balouch *et al.*** [5], found that bradycardia was observed more than tachycardia in the studied patients, but agreed with the current study as regard development of prolonged QT interval in (17.0%) pf patients.

The mean of QT interval was 325.40 ± 50.92 (msec) and mean of the QTc was 416.03 ± 59.95 (msec). Prolonged QTc interval was observed in (17.0%).

In a study done by **Akdur *et al.*** [19] the mean of QTc was 403±36 msec and prolonged QTc was the most recorded type of arrhythmia present in (53.7%) of patients. In the current study, QT interval and QTc duration were significantly increased with mortality where they were longer in died than discharged patients (288.67 ± 51.38 vs 352.43 ± 57.47, P=0.007, and 398.49 ± 57.25 vs 527.71 ± 106.05, P=0.002) in recovered and died patients respectively.

The present study agreed with **Liu *et al.*** [20] who observed that the mean of QTc was significantly higher (503±41) in non survivors than in survivors (432.71±51.21).

It was observed in the current study that there was a significant association between development of arrhythmias like sinus tachycardia, and prolonged QTc and the outcome of the studied cases where these arrhythmias were more among died than recovered patients (P=0.010, and 0.028) respectively.

This may be due to the presence of different predisposing factors for QT prolongation and progression to more severe type of arrhythmia that need close observation and care to the poisoned patient like: older ages, female gender, low left ventricular ejection fraction, left ventricular hypertrophy, ischemia and electrolyte abnormalities including hypokalemia and hypomagnesaemia [21]**.**
Shadnia *et al.* [22] and **Liu *et al.*** [20] agreed with the present study as regard considering the prolonged QTc interval to have the strongest prognostic value in OP poisoning and also as mortality predictor.

There was high statistically significant increase in the mean of CRP, and cardiac enzymes including (Troponin (migram/L), CPK (U/L)) level in died patients as compared to recovered ones (P<0.001, for all).

The mean of CRP level was highest in died patients. This was in agreement with the results of **Wu *et al.*** [23] study where they also found significant association between the CRP level and the patients' prognosis.
Tsai *et al.* [24] also observed significant relationship between the CRP level and the severity of the cases where the higher the level the higher the severity grade. CRP is an important component of the immune system. It is a reactive substance that is elevated in acute injury and inflammation. It is also used to monitor the autoimmune and infectious diseases. During the acute phase response, the levels of CRP rapidly increase within 2 hours of acute insult, reaching a peak at 48 hours [25]**.**
Sen *et al.* [25] found ″strong positive correlation between high CPK level and the severity of poisoning, so that it can be used as a predictor of outcome in OP poisoning″. In contrast, **Khan *et al.*** [26] found that there was no relation between CPK and patients' severity and mortality.

In this study, it was found that (91.25%) of the cases were recovered and returned to home, versus seven cases (8.75%) were died; four cases were died due to cardiac arrest, and three cases were died by pneumonia.
By using univariate logistic regression analysis for prediction of death among our studied participants, it was found that older age, higher dose (cc), abnormal vital signs (blood pressure, heart rate, and

respiratory rate), abnormal ECG finding (QT, QTc, and sinus tachycardia), raised liver and kidney functions were significantly increased among died patients.

By using the multivariate logistic regression "Backward regression" analysis, we found that only older age and raised liver functions as significant predictors of mortality among the studied cases (OR=38.836, 95%CI= 2.381 - 633.335, P= 0.010, and OR=18.220, 95%CI= 1.318 - 251.816, P= 0.030) respectively.

In conclusion, Acute OPP can be associated with severe cardiac complications within few hours of exposure including myocardial infarction. ECG grading is a predictor for both primary and major adverse outcome of patients with acute OPP. The corrected QT interval could be considered as an excellent parameter to predict morbidity and mortality in patients with acute OPP and it was an alarming sign of major outcome in patients with acute OPP. Serum cardiac Tn-I level could be considered an effective predictor of direct myocardial toxic effect induced by OPCs. Moreover, the ability of severe OPP to cause direct myocardial injury apart from rhythm disturbances was assured.

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