CORRELATION BETWEEN METHEMOGLOBINEMIA, PSEUDOCHOLINESTERASE LEVEL, TROPONIN I LEVEL, AND ALUMINIUM PHOSPHIDE POISONED PATIENTS' OUTCOMES

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ABSTRACT

Background: Phosphide poisoning is becoming a more prevalent self-poisoning compound in Egypt. Within the first 12 to 24 hours after phosphide exposure, most deaths happen, mainly because of cardiovascular toxicity. Peripheral vascular failure and myocardial ischemia are listed as the causes of mortality in these patients; however, the underlying mechanisms are still unclear. **Aim of the Work:** This study aimed to determine the magnitude of cardiovascular affection in patients who were intoxicated with aluminum phosphide (ALP) and to assess the role of some investigational parameters such as levels of methemoglobin (Met-Hb), pseudocholinesterase (PCE), and troponin I (Tn-I) as predictors for mortality and their correlation with patients' outcomes. **Subjects and Methods:** A clinical prospective comparative study between survivors and non-survivors was conducted on 60 ALP-intoxicated patients of both sexes who were admitted to "The Toxicology Unit of Emergency Hospital Mansoura University, Egypt. **Results:** There were highly statistically significant differences between survivors and non-survivors regarding Met-Hb, and Tn-I levels with no statistically significant differences regarding PCE level. Met-Hb and Tn-I were more sensitive and more specific than PCE in differentiating non-survived cases. **Conclusions:** It can be concluded that there is a strong correlation between the rise in blood levels of Met-Hb and Tn-I levels in ALP-poisoned patients. In addition, both could be used as predictors of mortality and differentiation of cases with poor prognosis at the time of admission in such highly fatal poisoning.

Keywords: *Aluminum Phosphide, Poisoning, Met-Hb, PCE, Troponin-I.*

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INTRODUCTION

Aluminum phosphide (ALP) pesticides are frequently employed as grain preservatives. It is a serious health issue with a high death rate, particularly in underdeveloped nations due to its accessibility and low cost ***(Mehrpour et al., 2008; Louriz et al., 2009)***. Phosphide poisoning is becoming a more prevalent self-poisoning compound in Egypt ***(El Naggar and El Mahdy, 2011)***.

Phosphides are typically found in the form of zinc or ALP as powders or pellets. For many years phosphide compounds have been employed as pesticides to safeguard grains while being transported and stored. When phosphides encounter acids or combine with atmospheric moisture, they generate lethal phosphine gas ***(Mehrpour et al., 2012)***. These substances can cause acute poisoning either directly by salt ingestion or indirectly through inadvertently breathing phosphine gas produced during allowed usage ***(Proudfoot, 2009)***.

Once consumed, phosphides are broken down by the stomach's diluted hydrochloric acid content into extremely poisonous phosphine gas ***(Popp et al., 2002)***. As a respiratory toxin, phosphine blocks the cytochrome C oxidase enzyme, preventing mitochondrial oxidative phosphorylation ***(Singh et al., 2006)***. In addition, it results in a significant decrease in mitochondrial membrane potential, disrupts the architecture of the mitochondria, and slows oxidative respiration by 70%. Moreover, the extremely reactive hydroxyl radical can be created by the reaction of phosphine with hydrogen peroxide. Furthermore, phosphine inhibits peroxidase and catalase, which leads to lipid peroxidation and hydroxyl radical-associated damage ***(Proudfoot, 2009)***.

Due to phosphine gas's rapid and easy absorption, there is a brief time lag between ingesting it and the onset of systemic manifestations ***(Gurjar et al., 2011)***. Most organs, including the heart, lungs, kidneys, and gastrointestinal system, are impacted by phosphide toxicity. Early signs and symptoms include breath smells like garlic, nausea, vomiting, dyspnea, retrosternal and epigastric pain, anxiety, and agitation. Furthermore, the two most important early indicators of toxicity are peripheral circulatory collapse and shock ***(Mostafazadeh, 2012)***. Delayed esophageal stricture, Hepatitis, acute tubular necrosis, and hemolysis are uncommon and rare side effects of phosphide poisoning ***(Lakshmi, 2002; Shadnia and Soltaninejad, 2011)***.

Within the first 12 to 24 hours, most deaths happen, mainly because of cardiovascular toxicity. Peripheral vascular failure and myocardial ischemia are listed as the causes of mortality in these patients; however, the underlying mechanisms are still unclear ***(Jadhav et al., 2012)***. It manifests as congestive heart failure with refractory hypotension, electrocardiographic (ECG) abnormalities with elevation of cardiac markers, such as creatine phosphokinase- MB (CPK-MB) and Troponin I (Tn-I) ***(Nakakita et al., 2009)***. Troponin level indicates very early the existence of cardiotoxicity and reflects microscopic myocardial necrosis. Additionally, Tn-I has a high specificity for muscle damage in the heart ***(Thygesen et al., 2012)***.

Severe methemoglobinemia after ALP intoxication has been reported due to the oxidization of hemoglobin ferrous iron to the ferric form leading to methemoglobin (Met-Hb) production ***(Lakshmi, 2002)***. The reduced ability of Met-Hb to supply sufficient oxygen to tissues could be an additional factor contributing to multiple organ failure after an ALP overdose ***(Aggarwal et al., 1999)***.

Pseudocholinesterase (PCE) activity inhibition has been documented in animal studies after acute ALP poisoning ***(Anger et al., 2000)***. One of the proposed mechanisms of toxicity is the reduction of the true cholinesterase and serum cholinesterase enzymes, but they usually do not show obvious clinical manifestations ***(Mittra et al., 2001)***.

THE AIM OF THE WORK

The purpose of this study is to determine the magnitude of cardiovascular affection in patients who were intoxicated with ALP and to assess the role of some investigational parameters (Met-Hb, PCE, and Tn-I) as predictors for mortality and their correlation with patients' outcomes.

SUBJECTS AND METHODS

Study Design:

A clinical prospective comparative study between survivors and non-survivors was conducted on 60 ALP-intoxicated patients of both sexes who were admitted to "The Toxicology Unit of Emergency Hospital Mansoura University, Egypt" during the period between 1st July 2021 to 1st July 2023.

Ethical Considerations:

The code number *(R.21.05.1341)* was assigned to the acceptance from the Institutional Review Board, Mansoura University's Faculty of Medicine. All participants or their legal guardians provided informed written consent. Giving each patient a code number kept the data confidential throughout the study period.

Inclusion criteria:

The study comprised subjects (age 12 years or older) who had a history of ALP tablet consumption and manifested within 6 hours of exposure without prior medical therapy in any hospital or health care unit before admission.

Exclusion criteria:

Patients who had received treatment in any medical center before admission, non-manifested subjects, patients with doubtful ingestion, patients with multiple concurrent poisoning, patients younger than 12 years old, and patients who declined to give consent were all excluded from the study. The study excluded patients having a history of diabetes mellitus, heart conditions, and other chronic illnesses. Additionally, any patients with chronic liver disorders, pregnancy, or the use of carbamates or organophosphates and other factors known to alter PCE levels were not included. Cases with a history of drugs that cause methemoglobinemia were also excluded.

Study Enrollment Procedures:

Every patient underwent a detailed history taking that included age, gender, place of residence, occupation, mode and cause of poisoning, quantity and route of exposure, time passed before hospital admission, and past medical history. The compound's distinct smell, the usual clinical signs that appeared soon after exposure, and the trustworthy identification of the substance presented by the patient's attendants all confirmed the diagnosis. Vital signs monitoring, oxygen saturation (SO2%), and a general clinical evaluation were all recorded. Furthermore, the Glasgow coma scale (GCS), pupil size, cardiovascular examination with an electrocardiogram (ECG), and central venous pressure (CVP) measurement were used to assess the patient's clinical condition. Normal values were stated according to ***Rees et al. (2017)***.

Sampling:

Before administering any medication, all patients had blood samples taken upon admission. Five milliliters of venous blood samples were drawn in aseptic settings using standard Vacutainer test tubes. The serum samples were then separated for the assessment of Met-Hb, PCE, and cardiac Tn-I levels by centrifugation at 3000 rpm for 10 minutes, and then frozen at -20°C. Before the assay, samples were brought to room temperature.

Biochemical studies:

The following three biochemical analysis were studied:

I. Quantitative assessment of Met-Hb using "SunRed Enzyme-Linked Immunosorbent Assay Kit".
II. Quantitative assessment of PCE level using "Biochemical Enterprise Kits".
III. Quantitative assessment of cardiac Tn-I levels using "SunRed Enzyme-Linked Immunosorbent Assay Kit".

Treatment of phosphide poisoning:

Standard supportive treatment as well as initial stabilization measures were administered. Gastric lavage with a sodium bicarbonate solution was used to decontaminate the gut. Additionally, symptomatic treatment was administered based on the circumstances of the patient.

Outcome Measures:

Every patient was monitored until their death or hospital release. The primary outcomes were divided into survivors and non-survivors.

Statistical Analysis:

Data was collected, coded, and tabulated using IBM SPSS Corp. Released in 2013 for Windows, Version 22. Numbers and percentages were used to describe the qualitative data. The median and mean were used to describe quantitative data. The Kolmogorov-Smirnov test was used to characterize the standard deviation for parametric data following a normality test. Correlation analysis (using Spearman's method) was used to assess the strength of association between two quantitative variables. The results were evaluated for significance at the (0.05) level.

RESULTS

During the study period, 60 subjects of ALP poisoning presented to the "Toxicology Unit of Emergency Hospital Mansoura University" were divided into two groups: survivors' group [49 cases (81.7%)] and non-survivors' group [11 cases (18.3%)]. **Table (1)** shows the ***socio-demographic*** characteristics of ALP-poisoned cases according to the survival of the studied cases. The mean age of the survivors was 25.10±9.95 years and 22.36±7.93 years in non-survivors. Out of all poisoned patients, most of cases were males 36 cases (60 %), 38 cases (63.3%) were from rural areas, 30 cases (50%) were students, 45 cases (75%) were due to family troubles and 15 cases (25%) were due to financial causes. All cases had ingested recently opened tablets as a suicidal manner of poisoning. There was no history of medical diseases nor psychiatric troubles with no statistically significant difference between both groups regarding the socio-demographic characteristics.

Table (2) shows the ***clinical presentation*** according to the survival of ALP-poisoned cases, 13 cases (26.5%) of survivors presented with garlic odor while all non-survivors presented with garlic odor with highly statistically significant differences between both groups (P<0.001**). The mean number of tablets ingested by survivors was half a tablet and 1 tablet in non-survivors with

highly statistically significant differences between both groups (P<0.001**). The mean time lag from ingestion to medical attention was about 1 hour in survivors and 1.5 hours in non-survivors with no statistically significant differences between both groups (P=0.053). Most ALP poisoning cases were presented with gastrointestinal tract manifestations, vomiting occurred in [57 cases (95%)] and abdominal pain in [58 cases (96.6%)] with no statistically significant differences between both groups (P=1.0). Hematemesis occurred in 2 cases (4.1%) of survivors with no statistically significant differences between both groups (P=1.0). Diarrhea occurred in 18 cases (36.7%) of survivors, and in 10 cases (90.9%) of non-survivors with highly statistically significant differences between both groups (P<0.001**). All cases in both groups were presented with normal-sized pupil (2-4 mm in light). The median of GCS in survivors was (score 15) and in non-survivors was (score 14), the median of CVP in survivors was (11 mmHg) and in non-survivors was (27 mmHg) with highly statistically significant differences between both groups regarding GCS and CVP values (P<0.001**).

Table (3) shows the ***vital signs*** of ALP-poisoned cases according to the survival of the studied cases, there were highly statistically significant differences between survivors and non-survivors regarding pulse, systolic blood pressure, diastolic blood pressure, and respiratory rate. Tachycardia, hypotension, and tachypnea appeared to be more prominent in non-survivors with high statistically significant differences (P<0.001**).

Table (4) shows the ***ECG and Echocardiographic changes*** in ALP-poisoned cases according to the survival of the studied cases. Regarding ***ECG changes,*** 27 cases (55.1 %) of survivors were normal ECG and all non-survivors showed ECG changes in the form of atrial fibrillation (AF) in 7 cases (63.6%), wide complex ventricular tachycardia (>120 millisecond) in 3 cases (27.3%) and sinus tachycardia (100-150 beats/minute) in one case (9.1%) with highly statistically significant differences between both groups (P<0.001**). Regarding ***Echocardiographic changes***, 37 cases (75.5%) of survivors showed normal echocardiography, while all non-survivors showed echocardiographic changes in the form of mild global hypokinesia in 3 cases (27.3%) and severe global hypokinesia in 8 cases (72.7%) with highly statistically significant differences between both groups (P<0.001**).

Table (5) shows the ***vasopressor (VP), assisted ventilation need and average intensive care unit (ICU) stay*** in the studied ALP-poisoned cases according to the survival of the cases. Regarding ***VP*** to improve the shock, 40 cases (81.6%) of survivors did not need VP while all non-survivors needed it. About 8 cases (72.7%) of non-survivors needed Noradrenaline with Dopamine infusion and 3 cases (27.3%) needed adrenaline infusion along with Noradrenaline and Dopamine regimen with highly statistically significant differences between both groups (P<0.001**). Regarding ***endotracheal intubation (ETI)*** and ***mechanical ventilation (MV),*** 47 cases (95.9%) of survivors did not need ETI nor MV while all non-survivors needed ETI and MV with highly statistically significant differences between both groups (P<0.001**). Regarding ***ICU s***tay, in survivors, the mean ICU stay was about 5 days and ≤ 1 day in non-survivors with highly statistically significant differences between both groups (P<0.001**).

Table (6) shows ***PCE, Met-Hb, and Tn-I levels*** according to the survival of the studied ALP-poisoned cases, there were highly statistically significant differences between survivors and non-survivors regarding Met-Hb, and Tn-I levels (P<0.001**) with no statistically significant differences regarding PCE level (P=0.667).

Figures (1) and (2) show that ***Met-Hb*** and ***Tn-I*** were more sensitive and more specific than PCE in differentiating non-survived cases using the Receiver Operating Characteristic (ROC) curve analysis.

Table (7) shows that ***Met-Hb*** and ***Tn-I*** were 90.9 % and 81.8% sensitivity respectively and both were 95.9% specificity by using Area Under Curve (AUC), Positive Predictive Value (PPV) and Negative Predictive Value

(NPV) with highly statistically significant differences between both groups (P<0.001**). **Figure (3) and Table (8)** show the ***correlation coefficients between Met-Hb and Tn-I levels*** among the studied ALP-poisoned cases, it was found to be (r=0.896) with a statistically significant positive correlation (P<0.001**).

Figure (4) shows the ***outcome*** of the studied ALP-poisoned cases**;** the mortality rate was about 18.3% among the total cases. **Table (9)** shows that ***Met-Hb*** and ***Tn-I*** levels were statistically significant differences (P=0.01* and 0.005* respectively) in the prediction of death at the time of admission among the studied ALP-poisoned cases.

Table (1): Socio-demographic characteristics according to the survival of the studied ALP-poisoned cases.

Variables	Survivors n=49 (81.7%)	Non-Survivors n=11 (18.3%)	Test of Significance	P-value
Age/years Mean ± SD	25.10±9.95	22.36±7.93	t=0.852	P=0.398
Sex Male Female	27 (55.1%) 22 (44.9%)	9 (81.8%) 2 (18.2%)	χ^2=2.67	P=0.102
Residence rural urban	31 (63.3%) 18 (36.7%)	7 (63.6%) 4 (36.4%)	χ^2=0.001	P=0.982
Occupation Worker Student Housewife Farmer	7 (14.3%) 26 (53.1%) 8 (16.3%) 8 (16.3%)	3 (27.3%) 4 (36.3%) 2 (18.2%) 2 (18.2%)	MC	P=0.695
Cause of poisoning Financial causes Family troubles	13 (26.5%) 36 (73.5%)	2 (18.2%) 9 (81.8%)	χ^2=0.334	P=0.563

*N: number, SD: Standard Deviation, t: Student's t-test, χ^2: Chi-Square test, MC: Monte Carlo test. *Statistically significant if P≤0.05 and **highly significant if P≤0.001.*

Table (2): Clinical presentation according to the survival of the studied ALP-poisoned cases.

Variables	Survivors n=49 (81.7%)	Non-Survivors n=11 (18.3%)	Test of significance	P-value
Odor No odor Garlic odor	36 (73.5%) 13 (26.5%)	0 11(100%)	χ^2=20.20	P<0.001**
Number of ingested tablets (min-max)	0.5 (0.5-2.0)	1.0 (1.0-2.0)	Z=4.23	P<0.001**
The time lag from ingestion to medical attention (hs)(min-max)	1.0 (0.5-2.0)	1.5 (1.0-4.0)	Z=1.93	P=0.053
Presenting complaints Hematemesis Vomiting Diarrhea Abdominal pain	2 (4.1%) 46 (93.9%) 18 (36.7%) 47 (95.9%)	0 11 (100%) 10 (90.9%) 11 (100%)	FET FET χ^2=10.59 FET	P=1.0 P=1.0 P=0.001** P=1.0
Pupil size (mm) Normal pupil size (2-4 mm in light)	49 (100%)	11 (100%)	χ^2=0	P=1.0
GCS (Score 3-15) (min-max)	15 (14-15)	14 (10-15)	Z=-4.982	P<0.001**
CVP (mmHg) (min-max)	11 (7-30)	27 (16-32)	Z=-4.416	P<0.001**

*n: number, min: minimum, max: maximum, hs: hours, mm: millimeter, GCS: Glasgow Coma Score, CVP: Central Venus Pressure, mmHg: millimeters of mercury, χ^2: Chi-Square test, FET: Fischer Exact Test, Z: Mann Whitney U test. *Statistically significant if P≤0.05 and **highly significant if ≤0.001.*

Table (3): Vital signs according to the survival of the studied ALP-poisoned cases.

Variables (Mean ± SD)	Survivors n=49 (81.7%)	Non-Survivors n=11 (18.3%)	Test of significance	P value
Pulse rate / min	100.26±19.53	128.64±8.69	t=4.69	P<0.001**
Systolic blood pressure (mmHg)	99.08±19.25	71.82±11.24	t=4.51	P<0.001**
Diastolic blood pressure (mmHg)	60.53±14.07	40.36±10.98	t=4.45	P<0.001**
Respiratory rate /min	23.45±5.14	31.91±3.94	t=5.12	P<0.001**
Temperature (°C)	37.5±0.0	37.5±0.0	t=0	P=1.0

*n: number, SD: Standard Deviation, min: minute, mmHg: millimeters of mercury, °C: degree Celsius, t: Student's t-test. *Statistically significant if P≤0.05 and **highly significant if P≤0.001.*

Table (4): Electrocardiographic and Echocardiographic changes according to the survival of the studied ALP-poisoned cases.

Variables	Survivors n=49 (81.7%)	Non-Survivors n=11(18.3%)	Test of significance	P value
ECG				
Normal	27(55.1 %)	0	MC	P<0.001**
Sinus tachycardia	13(26.5%)	1(9.1%)		
Wide complex ventricular tachycardia	3(6.1%)	3(27.3%)		
Non-specific ST depression	2(4.1%)	0		
Diffuse ST elevation	2(4.1%)	0		
AF	2(4.1%)	7(63.6%)		
Echocardiography				
Normal	37(75.5%)	0	MC	P<0.001**
Mild global hypokinesia	4(8.2%)	3(27.3%)		
Severe global hypokinesia	8(16.3%)	8(72.7%)		

*n: number, ECG: Electrocardiography, AF: Atrial Fibrillation, MC: Monte Carlo test. *Statistically significant if P≤0.05 and **highly significant if P≤0.001.*

Table (5): Vasopressor, Intubation/Mechanical Ventilation needs, and average ICU stay according to the survival of the studied ALP-poisoned cases.

Variables	Survivors n=49(81.7%)	Non-Survivors n=11(18.3%)	Test of significance	P value
VP needs				
No need	40(81.6%)	0		
Noradrenaline + Dopamine	9(18.4%)	8(72.7%)	MC	P<0.001**
Noradrenaline + Dopamine +Adrenaline	0	3(27.3%)		
ETT/MV need				
No need	47(95.9%)	0		P<0.001**
ETT/MV	2(4.1%)	11(100%)	MC	
Average ICU stay (days) (min-max)	5.0 (3.0-25.0)	0.25 (0.08-1.0)	Z=5.48	P<0.001**

*n: number, VP: Vasopressor, ETT: Endotracheal Tube, MV: Mechanical Ventilation, ICU: Intensive Care Unit, min: minimum, max: maximum, MC: Monte Carlo test, Z: Mann Whitney U test. *Statistically significant if P≤0.05 and **highly significant if P≤0.001.*

Table (6): Pseudocholinesterase, Methemoglobin, and Troponin I levels according to the survival of the studied ALP-poisoned cases.

Variables Median (min-max)	Survivors n=49(81.7%)	Non-Survivors n=11(18.3%)	Test of significance	P value
PCE (IU/L) (min-max)	7281 (1033-11770)	7050 (5000-11820)	Z=0.430	P=0.667
Met-Hb (µmol/L) (min-max)	19 (4.3-97.8)	98 (69.5-178.2)	Z=4.96	P<0.001**
Tn-I (pg/ml) (min-max)	22 (10-978)	938 (653-999)	Z=4.73	P<0.001**

*n: number, min: minimum, max: maximum, PCE: Pseudocholinesterase, Met-Hb: Methemoglobin, Tn-I: Troponin I, IU/L: International Unit/Liter, µmol/L: micromole/Liter, pg/ml: picogram/milliliter, Z: Mann Whitney U test. *Statistically significant if P≤0.05 and **highly significant if P≤0.001.*

Table (7): The validity of Pseudocholinesterase, Methemoglobin, and Troponin-I levels in differentiating non-survived ALP-poisoned cases.

Variables Median (min-max)	AUC (95%CI)	P-Value	cut off point	Sensitivity %	Specificity %	PPV %	NPV %	accuracy %
PCE (IU/L)	0.542 (0.356-0.728)	0.667	7813.5	72.7	49.0	24.2	88.9	53.3
Met-Hb (µmol/L)	0.981 (0.954-1.0)	<0.001**	80.4	90.9	95.9	83.3	97.9	95.0
Tn-I (pg/ml)	0.959 (0.910-1.0)	<0.001**	893.50	81.8	95.9	81.8	95.9	93.3

*n: number, min: minimum, max: maximum, PCE: Pseudocholinesterase, Met-Hb: Methemoglobin, Tn-I: Troponin I, IU/L: International Unit/Liter, µmol/L: micromole/Liter, pg/ml: picogram/milliliter, AUC: Area Under Curve, CI: Confidence interval, PPV: Positive Predictive Value, NPV: Negative Predictive Value. *Statistically significant if P≤0.05 and **highly significant if P≤0.001.*

Table (8): The correlation between Methemoglobin and Troponin-I levels among the ALP-poisoned studied cases.

		Met-Hb (µmol/L)
Tn.1 (pg/ml)	r	0.896
	p	<0.001**

*Met-Hb: Methemoglobin, Tn-I: Troponin I, µmol/L: micromole/Liter, pg/ml: picogram/milliliter, r: Spearman correlation coefficient. *Statistically significant if P≤0.05 and **highly significant if P≤0.001.*

Table (9): Methemoglobin and Troponin-I levels as predictors of death at the time of admission among the studied ALP-poisoned cases.

Variables	Standardized coefficient β	P-value	Odds ratio	(95% CI)	
				Lower limit	Upper limit
Met-Hb (µmol/L)	0.104	0.01*	1.11	(1.02-1.20)	
Tn-I (pg/ml)	0.01	0.005*	1.01	(1.003-1.018)	

*Met-Hb: Methemoglobin, Tn-I: Troponin I, µmol/L: micromole/Liter, pg/ml: picogram/milliliter, CI: confidence interval. *Statistically significant if P≤0.05 and **highly significant if P≤0.001.*

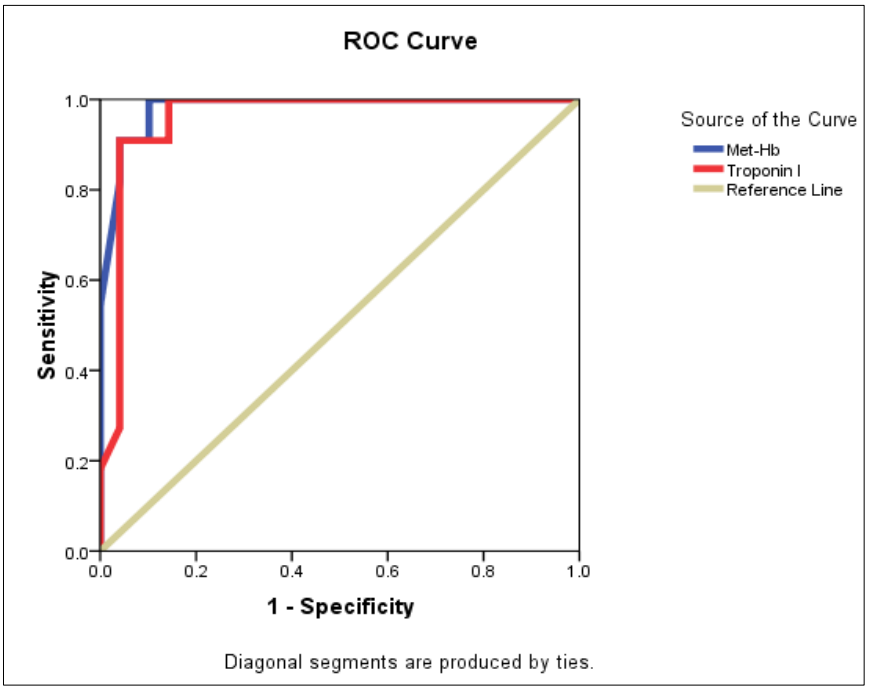

Figure (1): ROC curve of Methemoglobin and Troponin-I in differentiating non-survived ALP-poisoned cases.

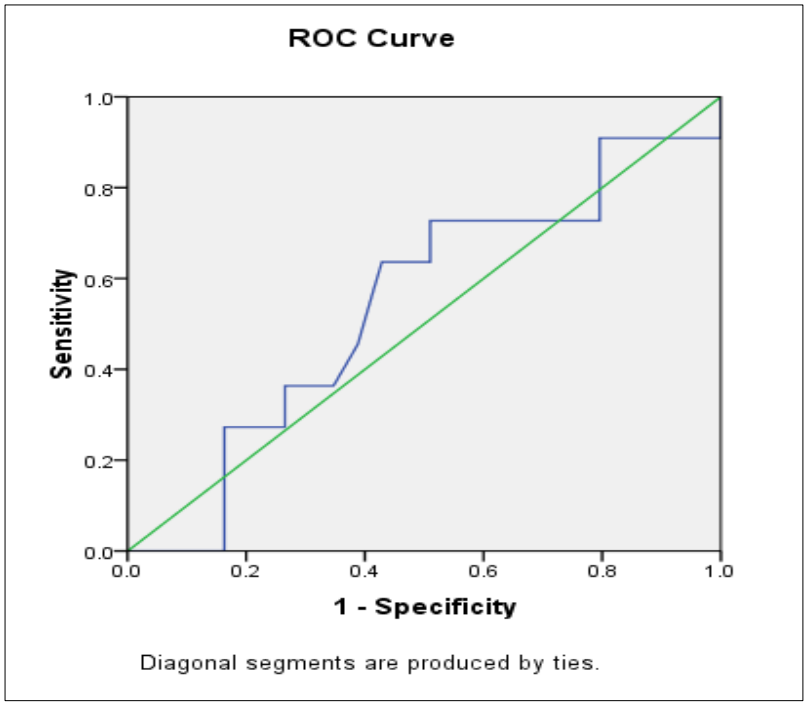

Figure (2): ROC curve of Pseudo-cholinesterase in differentiating non-survived ALP-poisoned cases.

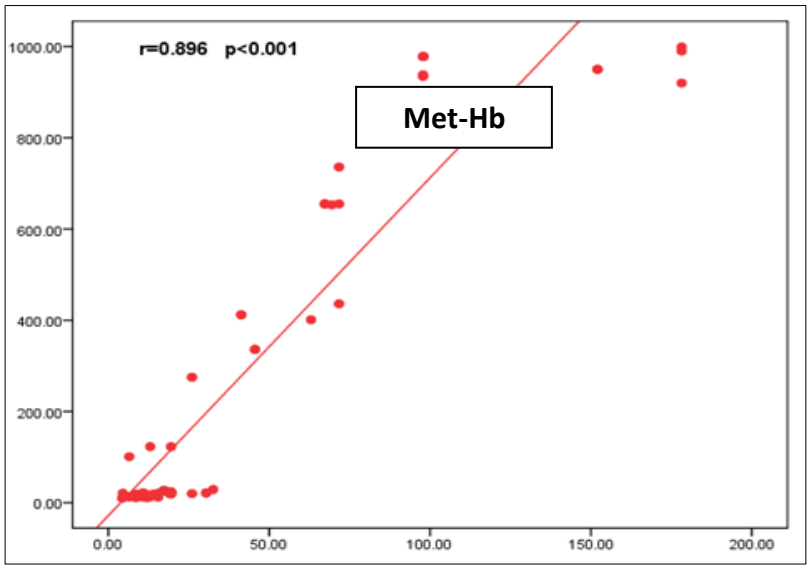

Figure (3): Scatter diagram showing the correlation between Methemoglobin level (µmol/L) and Troponin I level (pg/ml) among the studied ALP-poisoned cases.

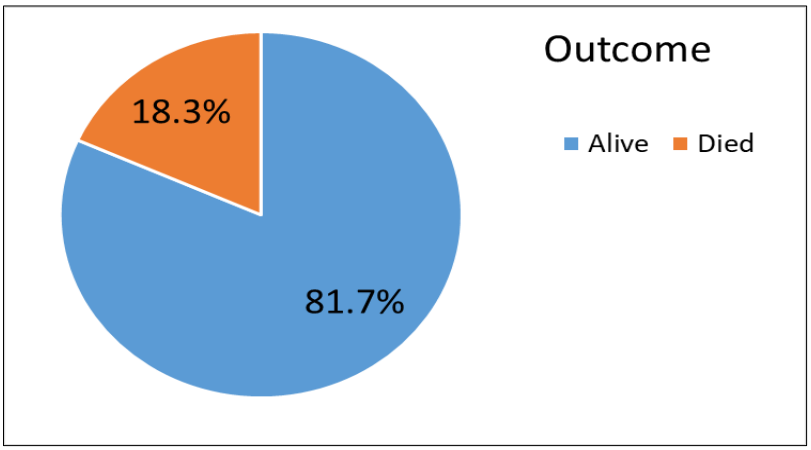

Figure (4): Outcomes of the studied ALP-poisoned cases.

DISCUSSION

Fumigants and rodenticide ALP are widely used, particularly in developing nations like Egypt and India ***(El Naggar and El Mahdy, 2011)***. Acute ALP poisoning is a fatal poisoning that typically has suicidal intent. When exposed to moisture, it emits an extremely deadly gas, which has a 90% fatality rate and there is currently no known counteragent for this gas ***(Ramezani et al., 2018; Sedaghattalab, 2022)***.

Numerous research works discuss the fundamental causes of toxicity caused by phosphine, but the precise process is still unknown ***(Prabhu et al., 2016)***. The present study tries to take a further step to figure out the underlying mechanism of the associated high mortality rate by investigating the magnitude of cardiotoxicity and myocardial damage determined by Tn-I level and evaluating the role of methemoglobinemia and pseudo-cholinesterase inhibition in induction of serious cellular hypoxia that add to the tremendous toxic effect of phosphine gas.

In the current study, 60 patients with acute ALP poisoning were included. Regarding the ***socio-demographic data*** characteristics, the mean age of the survivors was 25.10±9.95 years and 22.36±7.93 years for non-survivors. These results are in close agreement with those obtained by ***Mashayekhian et al. (2016)*** and ***Wahdan and Elmadah (2016)***, who reported that the mean age of their phosphide-poisoned patients was 24.7±9.6 and 24.5±11 respectively.

Regarding the sex of the cases, 60% of the patients were male which agrees with those obtained by ***Hassanian-Moghaddam et al. (2014)*** and ***Abdel-Hady et al. (2019)*** where 61.2% and 63.3% of their phosphide-poisoned poisoned patients were male respectively. This could be explained by the easy accessibility of males to these toxic tablets due to their work in agriculture as 63.3% of the studied cases were from rural areas.

Abdel-Hady et al. (2019) showed that 81.8% of their patients were also from rural areas. This may be related to the increased incidence of illiteracy and the easy availability of ALP tablets in the agricultural community. Additionally, the usage of ALP tablets for seed preservation is more prevalent in rural than in urban settings ***(Yatendra et al., 2014)***.

All subjects in this study have ingested phosphides in an intended suicidal attempt, 50% were students and 75% were due to family troubles. These findings are similar to those obtained by ***Shahin et al. (2016)*** who reported that 96.6% of their patients have intentionally ingested phosphides due to lack of family support. The raised prevalence of acute ALP intoxication in younger age groups may be attributed to their tendency to be easily excited and depressed as reported by ***Chaudhary et al. (2013)***.

Regarding the ***clinical presentation,*** 26.5% of survivors presented with garlic odor while all non-survivors presented with garlic odor with highly statistically significant differences between both groups. This can be explained by the large toxic ingestion of non-survivors as 1 g of phosphine gas with a fishy or garlic odor is released by a 3 g ALP tablet ***(Bogale et al., 2021)***.

According to ***Hashemi-Domeneh et al. (2016)***, the patient's breath had an odor similar to spoiled fish, which could be considered an early sign of toxicity due to the rapid release of phosphine gas.

The average number of ingested tablets in survivors was about 0.5 tablet and 1 tablet in non-survivors with highly statistically significant differences between both groups. This agrees with ***Bogale et al. (2021)*** that the average number of ALP tablets taken in their studied cases was 1.2 (3.6 gm).

Most of the patients in this study sought medical advice within a short period, the average time from ingestion of ALP tablets till hospital arrival was about 1 hour in survivors and 1.5 hours in non-survivors. These outcomes closely match ***Shahin et al. (2016)*** and ***Wahdan and Elmadah, (2016)*** findings, they reported that pre-hospital stays ranged from two to three hours on average.

The brief time between exposure and hospital attendance in the cases under study could be explained by the corrosive effect of phosphine with the early appearance of gastrointestinal tract manifestations ***(Mostafazadeh, 2012)***. Even though the current study couldn't identify a statistically significant difference

between survivors and non-survivors regarding the mean time lag, this factor is crucial and considered an important aspect of patients' outcomes, as ***Anand et al. (2011)*** reported.

Most patients in this study were presented to the Emergency Hospital with gastrointestinal tract manifestations such as vomiting (95%) and abdominal pain (96.6%). Haematemesis occurred in 3.3% of cases mostly due to its corrosive action ***(Mostafazadeh, 2012)***. In 90.9% of non-survivors and 36.7% of survivors, diarrhea was reported, with a large statistically significant difference between the two groups. This could be clarified by the hazardous effects of diarrhea on body fluid and resulting electrolyte disturbance that affects ventricular membrane stabilization and blood pressure.

Hosseinian et al. (2011) and ***Vijayanath et al. (2011)*** similarly noted that nausea, vomiting, and abdominal discomfort were the most typical symptoms seen by patients suffering from ALP poisoning.

In certain instances, the conscious state was compromised during the initial hospital presentation with normal bilateral pupillary size in both groups (2-4 mm in light). The median of GCS in survivors was (score 15) and in non-survivors was (score 14), with highly statistically significant differences between both groups. Moreover, the conscious level had changed dramatically in non-survivors. It was observed also that the median of CVP in survivors was (11 mmHg) and in non-survivors was (27 mmHg) at the initial time of presentation with highly statistically significant differences between both groups indicating rapid progressive development of heart failure and cardiogenic shock that impaired conscious level and cause hemodynamic instability.

The depth of coma is an important factor in ALP-poisoned patients' outcomes as mentioned by ***Sulaj et al. (2015)***. More than 50% of ALP-poisoned cases in the study conducted by ***Abdel-Hady et al., (2019)***, were presented with a GCS (13-15).

Furthermore, ***Hashemi-Domeneh et al. (2016)*** have mentioned that the degree of CNS affection won't be prominent unless an important complication occurs such as marked hypotension with subsequent cellular hypoxia. They also reported that adult respiratory distress syndrome (ARDS) and pulmonary edema have been observed in all non-survivors in which the mean CVP value was (24.3± 6).

Regarding the ***vital signs***, tachycardia, hypotension, and tachypnea appeared to be more prominent in non-survivors with high statistically significant differences. According to ***Katwal et al. (2021)***, refractory shock occurs in 60–100% of instances of ALP poisoning and is caused by phosphine's direct effects on blood arteries, adrenal glands, and cardiac myocytes.

Several ***ECG changes*** have been observed in the studied cases with high statistically significant differences between survivors and non-survivors. About (90.9%) of non-survivors have suffered from serious cardiac dysrhythmias in the form of AF (63.6%) and ventricular tachycardia (27.3%). On the other hand, most of the survivors (55.1%) had sinus rhythm, and (26.5%) had sinus tachycardia. These results are those reported by ***Agrawal et al. (2015)*** who observed that all non-survivors had cardiac arrhythmias, such as ventricular fibrillation (VF) and AF, while all survivors had sinus rhythm or sinus tachycardia. According to ***Abdel-Hady et al. (2019)***, patients with normal ECGs had a much lower death rate than patients with various types of arrhythmias. These authors also suggested that patients with ALP poisoning begin anti-arrhythmic medication as soon as possible.

Regarding the ***echocardiographic changes***, about 75.5 % of survivors have normal echocardiographic findings, and 24.5% suffer from global hypokinesia. In contrast, all non-survivors suffered from the dilated left ventricle with global hypokinesia and decreased ejection fraction (<40%). According to ***Mehrpour et al. (2012)*** and ***Yatendra et al. (2014)***, echocardiography of individuals poisoned with ALP may reveal increased ventricle size, left ventricular and septal up to global hypokinesia, decreased ejection fraction, and pericardial effusion with increased CVP.

The previous ECG changes and echocardiographic findings in patients

poisoned with ALP are thought to be the result of a direct harmful effect of phosphorus over myocardial contractility. It has been postulated that elemental phosphorus acts as a general protoplasmic poison interfering with the enzyme system leading to toxic myocarditis ***(Varghese et al., 2020)***.

Regarding the ***VP*** need, ***assisted ventilation***, and average ***ICU stay*** in the studied ALP-poisoned cases, 81.6% of survivors did not need VP while all non-survivors needed VP. The inhibition of mitochondrial cellular respiration and the ensuing generation of free radicals cause toxic myocarditis and congestive heart failure as well as the vasoplegia that occur due to direct toxic effects on the vascular tissue. Dopamine should be used as an inotropic support for poor hemodynamic conditions, while norepinephrine should be used for vasoplegia. ***Agrawal et al., (2015)*** reported that the cornerstones of the first-line therapy should be dopamine and norepinephrine.

About 95.9% of survivors did not need ***ETI*** or ***MV*** while all non-survivors needed ETI and MV. ALP poisoning has also been linked to pulmonary problems that call for intensive care. After 6-24 hours, ARDS may develop, there is also a chance of developing secondary bacterial pneumonia and chemical pneumonitis from pulmonary aspiration. Pulmonary edema typically necessitates MV and can worsen circulatory insufficiency. It might be noncardiogenic because of direct pulmonary cytotoxicity and potential small vessel damage ***(Faress et al., 2024)***.

Pannu, (2017) reported that both the need for VP and MV usually increase the ICU stay in ALP-poisoned patients. The range of ICU ***s***tay in the present study was (3-25 days) in survivors, in contrast, the maximum ICU stay was (1 day) in all non-survivors due to rapid death, with differences between the two groups that are extremely statistically significant regarding the VP need, assisted ventilation, and average ICU stay.

Most phosphide-intoxicated individuals passed away within the first 24 hours of exposure due to cardiotoxicity, considering the heart as a major target organ for phosphide toxicity ***(Sinha, 2018)***. A notable increase in troponin levels indicates myocardial damage. A tiny rise in troponin could be a sign of a microinfarction or a tiny area of myocardial necrosis. Furthermore, tachyarrhythmias and myocarditis have also been linked to increased troponin levels ***(Xue et al., 2014)***. Serum ***Tn-I level*** was measured in all studied cases on admission before administration of any medications to predict the degree of myocardial insult and cardiac affection. In contrast to survivors, non-survivors in the current study had a much higher serum Tn-I level, which suggests serious myocarditis and cardiac injury.

Methemoglobinemia after ALP poisoning is regarded as an unusual event as it was recorded in a few cases of ALP poisoning according to ***Lall et al. (2000); Lakshmi, (2002); Shadnia et al. (2011); Soltaninejad et al. (2011); Mostafazadeh et al. (2011); Wahdan and Elmadah, (2016)***. The oxidation of iron in haemoglobin (Hb) to the ferric state by free radicals is the mechanism of action of phosphine-induced methemoglobinemia. This results in reduced oxygen transport, histotoxic hypoxia, and a leftward shift in the oxygen dissociation curve ***(Shadnia et al., 2009)***.

Met-Hb levels are usually tested using CO-axial pulse oximetry with a direct correlation between Met Hb levels and symptoms ***(Iolascon et al., 2021)***.

Feiner et al. (2010) discovered that methemoglobin readings using CO- oximetry become increasingly erroneous as SaO_2 falls below 95% and the greatest accuracy was obtained in the 95% to 100% SaO_2 range rendering this approach unsuitable in hypoxic settings. Conversely, immunoassay plays a significant role in contemporary clinical laboratories and is not affected by hypoxic situations. Moreover, the assays' intrinsic potential for specificity and sensitivity is exploited by their ease of use ***(Hariri et al., 2022)***.

Met-Hb levels were measured in all studied ALP-poisoned cases using the immunoassay method. Met-Hb level was used to diagnose methemoglobinemia when it was > the reference range 9.3-37.2 µmol/L. The levels were tremendously exceeding normal within the first 6 hours of intoxication with statistically significant differences between

survivors and non-survivors. Moreover, it was observed that there was an association between Tn-I rise and Met-Hb levels in the studied cases with a statistically significant positive correlation**.** On the other hand, the mortality rate and the Met-Hb level were also found to be correlated by ***Iolascon et al. (2021)***. This may declare that the degree of myocardial injury might be directly related to subsequent methemoglobinemia that induces cellular hypoxia and increases the mortality rate.

The Met-Hb level can be lowered by a variety of treatments to acceptable levels or within the reference range. For methemoglobinemia, methylene blue is the recommended treatment in both clinical and experimental investigations ***(Iolascon et al., 2021)***.

While methylene blue is the primary antidotal therapy, other options include the use of ascorbic acid and N-acetylcysteine (NAC) could be used as adjuvant therapy. The production of reactive oxygen species and lipid peroxidation in biological systems is demonstrated to be one of the fundamental processes of ALP poisoning. Antioxidants are therefore still the primary treatment for ALP poisoning currently ***(Bianchi et al., 2021)***.

On the other hand, Trimetazidine as a cardioprotective drug may be promising in histotoxic hypoxia caused by methemoglobinemia. Trimetazidine decreases the beta-oxidation of fatty acids and increases the oxidation of glucose. Compared to the beta-oxidation of fatty acids, glucose oxidation uses less oxygen. Therefore, trimetazidine (one tablet of 35mg twice daily) aids in optimizing cellular energy generation in situations when the oxygen supply is limited by increasing glucose oxidation and decreasing the need for fatty acid metabolism ***(Ferrari et al., 2020)***.

Some researchers think that one of the main toxicity mechanisms of ALP is its effect on AChE activity**.** In the last several years, lots of studies have been done to determine how phosphine affects the amount and activity of AChE. Most of the findings indicated that ALP inhibits different mitochondrial enzymes; nonetheless, there was disagreement about a noteworthy decrease in AChE activity ***(Yadav et al., 2021)***.

Therefore, ***serum PCE level*** was measured in all ALP-poisoned patients in the current study, and it was found that the levels were within the normal range in survivors and non-survivors.

Abdelghafar et al., (2023*)** reported that phosphine exposure in humans and rats causes a significant reduction in PCE levels. However, phosphine exposure reduces PCE activity but does not lower brain AChE activity, according to a study by ***Sciuto et al. (2016). The results of the present study are similar to ***Afzali et al. (2019)*** who reported that phosphide poisons have a non-significant affection on PCE enzymes.

In addition, it was found that there were notable statistical differences between the groups of survivors and non-survivors regarding Met-Hb, and Tn-I levels with no statistically significant differences regarding PCE level. Moreover, Tn-I and Met-Hb levels were both more sensitive and more specific than PCE in differentiating non-survived cases using the ROC curve analysis. Therefore, we came to the belief that PCE activity cannot currently be used as a biomarker for phosphine exposure.

A systematic review and meta-analysis were conducted on Iran's ALP poisoning fatality rate. The pooled mortality rate of ALP poisoning in Iran was estimated to be 27.3% ***(Bagherian et al., 2021)***. Regarding the ***outcome*** of the studied ALP-poisoned cases; the mortality rate was about 18.3% among the total cases. Moreover, both ***Met-Hb*** and ***Tn-I*** levels showed statistically significant differences in the prediction of death among the studied ALP-poisoned cases.

CONCLUSION

It can be concluded that most phosphide-intoxicated individuals passed away within the first 24 hours of exposure due to cardiotoxicity considering the heart as a major target organ for phosphide toxicity. A tiny rise in Tn-I could be a sign of microinfarction or a tiny area of myocardial necrosis. High CVP at the time of presentation indicated rapid progressive development of heart failure and cardiogenic shock with serious myocarditis. The degree of myocardial injury might be directly related to methemoglobinemia which induces cellular

hypoxia increasing the mortality rate. There was a strong correlation between the rise in Met-Hb and Tn-I levels in ALP-poisoned patients. In addition, both could be used as predictors of mortality and differentiating cases with poor prognosis at the time of admission in such highly fatal poisoning. Moreover, PCE activity should not currently be used as a biomarker for phosphine exposure.

RECOMMENDATIONS

More extensive research on a large percentage of acute ALP poisoning cases is recommended. In clinical practice, continuous monitoring of cardiac condition by CVP measurements, ECG, and Echo consultation is very crucial in ALP poisoning management. Maintaining echo evaluation even after discharge of patients till regain myocardial normal wall motion is recommended. Using cardioprotective drugs such as Trimetazidine (TMZ) may be promising and need further studies. Owing to ALP-induced serious cardiac dysrhythmias, adding anti-arrhythmic medications as soon as possible is recommended. Dopamine should be used as an inotropic support for poor hemodynamic conditions, while norepinephrine should be added for vasoplegia. Evaluating Met-Hb levels using immunoassay is recommended rather than CO-oximetry especially in hypoxic settings. Studying the efficacy of methylene blue treatment for such cases is required to help decrease the mortality associated with such fatal poison, ascorbic acids, riboflavin, and N-acetylcysteine may be promising alternatives and need further studies. Moreover, healthcare providers must investigate the magnitude of cardiotoxicity and myocardial damage by Tn-I levels, they should be aware of methemoglobinemia presentation in ALP poisoning cases and realize the importance of (Met-Hb and Tn-I levels) as non-routine investigations in phosphide poisoning.

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العلاقة بين مستوي الميتهيموجلوبين وإنزيم الكولين إستيريز الكاذب والتروبونين آي فى الدم ونتائج المرضى المصابين بتسمم فوسفيد الألومنيوم

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الملخص العربى

المقدمة: التسمم بمركبات الفوسفيد أصبح من أكثر طرق الإنتحار شيوعاً في مصر. تحدث معظم حالات الوفيات خلال أول ١٢-٢٤ ساعة من التعرض للفوسفيد، ويرجع ذلك إلى تسمم القلب والأوعية الدموية على الرغم من أنه تم إدراج فشل الأوعية الدموية الطرفية ونقص تروية عضلة القلب كأهم أسباب الوفاة لدى هؤلاء المرضى إلا أن آلية حدوثها مازالت غير واضحة.

الهدف من العمل: تهدف هذه الدراسة إلى تحديد مدى تأثر القلب والأوعية الدموية في حالات التسمم الحاد بفوسفيد الألومنيوم وتقييم استخدام بعض الفحوصات مثل نسبة الميتهيموجلوبين ومستوي إنزيم الكولين إستيريز الكاذب و التروبونين آي في الدم في التنبؤ باحتمالية حدوث الوفاة وربطها بنتائج المرضى ووفياتهم.

خطة البحث: هذه دراسة مقارنة سريرية مستقبلية بين المرضى الناجين والمتوفيين. أجريت على ٦٠ مريضا تعرضوا للتسمم ب فوسفيد الألومنيوم من كلا الجنسين وترددوا على وحدة السموم بمستشفي الطوارئ الجامعي بمدينة المنصورة بمصر.

النتائج: كان هناك فرقا ذو دلالة إحصائية واضحة في مستويات الميتهيموجلوبين والتروبونين آي بين المرضى الناجين والمتوفيين وكذلك يمكن استخدام مستوى الميتهيموجلوبين والتروبونين آي فى الدم كمؤشر أكثر حساسية للتنبؤ بحدوث الوفيات الناجمة عن التسمم الحاد بفوسفيد الألومنيوم. ولكن لا توجد فروق ذات دلالة إحصائية فى مستوي إنزيم الكولين إستيريز الكاذب بين المرضى الناجين والمتوفيين

ومن هذه النتائج نستخلص الاتي: توجد علاقة قوية بين ارتفاع مستوى الميتهيموجلوبين والتروبونين آي في الدم في حالات التسمم الحاد بفوسفيد الألومنيوم. بالاضافة إلى أنه يمكن استخدامهم في التنبؤ بوفيات فوسفيد الألومنيوم.