Ain Shams Journal of Forensic Medicine and Clinical Toxicology
Jan 2020, 34: 51-68

Assessment of Intravenous Lipid Emulsion as an Adjuvant Therapy in Acute Aluminum Phosphide Poisoning: A randomized Controlled Trial

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Abstract

Background: Aluminum phosphide (ALP) is efficient rodenticide and insecticide. The increased incidence of acute ALP poisoning and its high mortality is a challenge for health professionals, there is no specific antidote and the treatment is mainly supportive. **Aim of the work:** The aim of this study was to evaluate the efficacy and safety of intravenous lipid emulsion as an adjuvant therapy for acute ALP poisoning. **Patients and methods:** The present study was carried out on fifty patients with acute ALP poisoning admitted at Poison Control Unit, Tanta University Emergency Hospital, throughout a period from the start of December 2016 till November 2017. The study participants were randomly allocated into 2 equal groups (25 patients each): The experimental group (received ILE 20% at a rate of 10ml/h IV infusion plus the conventional treatment of ALP poisoning), and the control group (received the conventional treatment only). **Results:** The number of deaths in the experimental group was lower than the control group, but it did not reach a significant level. The need for intubation and mechanical ventilation was significantly lower in the experimental group compared to the control group. **Conclusion:** The administration of ILE 20% in acute ALP poisoning at a rate of 10ml/h IV infusion is a safe therapy. Moreover, the adjuvant ILE use along with the conventional supportive treatment could have a therapeutic effect in ALP poisoned patients.

Key words Aluminum phosphide, grain tablet, intravenous lipid emulsion, clinical trial

Introduction

Aluminum phosphide (ALP) is one of the solid fumigant pesticides. In Egypt, ALP is extensively used to protect grains against insects and rodents. It is available in the form of tablets known as "grain tablet" (Rahman et al., 2017).

Suicidal ingestion of ALP tablets is obviously increasing in developing countries. This is attributed to its wide use, free availability in the market, and its low cost (Singh et al., 2014).

Aluminum phosphide reacts with water or acids to release the highly toxic phosphine gas. It inhibits mitochondrial cytochrome oxidase and cytochrome C, thereby it disrupts cellular respiration (Anand et al., 2013). Additionally, oxidative stress is one of the proposed mechanisms of phosphide toxicity (Sciuto et al., 2016).

Aluminum phosphide toxicity is extremely fatal. The conveyed mortality rate differs from 37-100%. More than 90% of patients die within the first 24 hours, mainly due to cardiac dysrhythmia. Despite continuous research, no effective antidote has been reported for this lethal poisoning so far (Meena et al., 2015).

PH_3 is phosphorus trihydride and solubility of phosphorus can effect PH_3. Solubilities of phosphorus are as follows: In water: 1 part/300,000 parts water; in absolute alcohol: 1 g/400 mL. One gram phosphorus dissolves in 80 ml olive oil, 60 ml oil of turpentine, and about 100 mL of almond oil. So, PH_3 might also have lipid soluble property and used IV lipid emulsion may counter its effects (Baruah et al., 2015).

Intravenous lipid emulsion (ILE) is a sterile fat emulsion prepared for intravenous administration as a source of calories and essential fatty acids. Its main components include up to 20% soybean oil, 1.2% egg yolk phospholipids, 2.25% glycerin, and water for injection. In addition, sodium hydroxide has been added

to adjust the PH, so that the final PH is 8 (Perez et al., 2009).

Based on animal models and clinical studies, ILE is an established antidote for local-anesthetic drugs systemic toxicity (Cave and Harvey, 2011). Furthermore, beneficial effects of ILE on Glasgow Coma Scale and metabolic profile in non-local anesthetic drug overdoses have been demonstrated (Taftachi et al., 2012). Besides, ILE has been well used for resuscitation of severe toxicities caused by various lipophilic non-local anesthetic drugs (Picard et al., 2014).

As regards ALP poisoning, ILE has been successfully used in resuscitation of two cases of suicidal poisoning with refractory hypotension as reported by Baruah et al. (2015). This promising effect of ILE has gained great attention. Accordingly, the aim of this study was to assess efficacy and safety of ILE as an adjuvant therapy of acute ALP poisoning.

Patients and methods

Study design, setting and ethical considerations:

This study was a randomized controlled trial (RCT); superiority trial with parallel design. The study participants were recruited from the Poison Control center Emergency Hospital, Tanta University starting from December 2016 till November 2017. The study was approved by the Research Ethical Committee, Faculty of Medicine, Tanta University. An informed written consent was obtained from each patient or his/her guardians (if the patient was unable to participate in the consent process). Confidentiality of the data was maintained by making a code number for each patient.

Eligibility criteria:

Inclusion criteria:

Male or female patients aged 12 years or older presented with symptomatic acute ALP poisoning. Diagnosis was made on the basis of:

1. History of exposure including reliable identification of the compound based on the container brought by patient's relatives.
2. The suggestive clinical manifestations following shortly after a single exposure to ALP.
3. Biochemical detection of phosphine gas in gastric aspirate which was taken immediately after inserting nasogastric tube and before gastric lavage was done by silver nitrate test. This test was done according to Wahab et al. (2008) as follow: Five ml of gastric aspirate and 15 ml of water are put in a flask and the mouth of the flask is covered by filter paper impregnated with 0.1N silver nitrate (16.987 g of silver nitrate in 1L distilled water). The flask is heated at 50^{o}C for 15 to 20 minutes; if phosphine is present the filter paper turns black.

Exclusion criteria:

- Patients less than 12 years of age.
- Pregnant and lactating women.
- Co -ingestion or exposure to other substances in addition to ALP.
- Patients had major medical conditions (e.g. cardiovascular disease, renal or hepatic failure)
- Patients presented more than 6 hours after ALP compound ingestion (late presenters)
- Patients received treatment in any hospital or medical center before admission.

Methods:

Fifty patients were randomly allocated into experimental and control groups (25 patients each) using the sequentially numbered, opaque sealed envelopes method. Where envelopes containing the treatment allocation were opened by the recruiting physician (Clark et al., 2016).

Control group:

The standard treatment only was given to the patients allocated in this group (25 patients) was provided as follows:

- Patient resuscitation including care of airway, breathing and circulation. Intravenous fluids and vasopressors (Norepinephrine) has been used to treat hypotension and refractory shock (Baeeri et al., 2013).
- Intubation and mechanical ventilation in the following conditions:
  Patients with Apnea, respiratory failure, Inadequate oxygenation (hypoxia), inadequate ventilation (hypercarbia), Disruption of the airway reflex, hemodynamically unstable and patients with disturbed conscious level(GCS <8) (Hua et al., 2017).
- Decontamination: Patients presented within 2 hours of ALP ingestion were subjected to gastric lavage using normal saline mixed with sodium bicarbonate solution (2 ampoules sodium bicarbonate 25% added to each 500cc saline), followed by a single (50 mg) dose of activated charcoal.
- For metabolic acidosis, intravenous sodium bicarbonate was considered.
- Magnesium sulfate: 1g IV infusion every 1hour for the first 3 hours, followed by 1–1.5 g every 6 hours for 24 hours (Gurjar et al., 2011).

Experimental group:

They received the standard treatment as mentioned in the control group .Additionally, they were administered SMOF Lipid 20% (Intravenous lipid emulsion 20% consists of a mixture of soybean oil, medium-chain triglycerides, olive- and fish-oil). It is produced by Fresenius Kabi USA company as IV infusion.

Based on the dose that has been successfully used by Baruah et al. (2015) to resuscitate two cases of severe aluminium phosphide intoxication, ILE was administered in this group at a rate of 10 ml/h, IV infusion continue until improvement or death of the patient. Both the triglyceride level and the clinical condition of the patient guided monitoring of the ILE infusion. The infusion rate was gradually tapered when improvement of the case has been observed

All patients were subjected to full history taking including age, gender, occupation, and level of education, circumstances of poisoning whether intentional or accidental, amount and route of exposure, time interval between exposure and beginning of treatment, and history of medical diseases such as liver, renal or cardiac diseases. Additionally, complete physical examination including vital signs, neurological examination including assessment of level of consciousness by Glasgow coma scale, cardiovascular examination including Electrocardiography (ECG), chest examination and abdominal examination.

Laboratory investigations:

Blood samples were obtained from each patient immediately after admission before giving any medications and repeated 12 hours after admission. Two samples were obtained, 1 milliliter arterial blood for blood gas analysis, and four milliliters venous blood for biochemical analysis including serum troponin I level, serum triglyceride level, serum sodium, potassium, and magnesium levels, blood urea and serum creatinine levels, serum alanine amino transferase (ALT) and aspartate amino transferase (AST), complete blood count, and random blood sugar level.

Outcome measures:

Primary outcome was mortality while secondary outcomes included mean arterial blood pressure that was assessed 12 hours after admission, the need for intubation and/or mechanical ventilation, duration of mechanical ventilation, the total dose of vasopressors, and the length of hospital stay.

All these data were collected in a special data sheet for every patient involved in the study.

Statistics:

Data were analyzed using Statistical Package for the Social Sciences (SPSS) for Windows, version 20.0 (SPSS, Chicago, IL, USA). For quantitative data, the Shapiro-Wilk test for normality was performed. For normally distributed data, values were expressed as mean ± standard deviation and Independent samples T test was applied. For data that were not normally distributed, median and interquartile range (expressed as 25^{th}-75^{th} percentiles) were calculated and Mann-Whitney U test was used for comparison between the studied groups. Concerning qualitative data, they were expressed as numbers and percentages and Pearson's Chi Square test or Fisher's Exact test when appropriate were used to examine association between two variables. In addition, Wilcoxon Signed Rank test was used to compare paired data that were assessed at admission and 12 hours later. Significance was adopted at $p < 0.05$ for interpretation of results of tests.

Results

Silver nitrate test:

Silver nitrate test was applied for all patients to detect aluminum phosphide, and it was positive in all (100%) the studied patients.

Sociodemographic, toxicity and clinical characteristics of the studied groups:

Baseline socio-demographic, toxicity and clinical characteristics of the studied patients at the time of admission were illustrated in tables (1,2 and 3). There were no significant differences between the experimental and control groups ($p>0.05$). All (100%) patients alleged suicidal ingestion of ALP tablets.

Laboratory investigations of the studied groups:

Tables (4 and 5) show the routine laboratory investigations of the studied groups at admission. Arterial blood gases (blood pH, P_aCO_2, HCO_3) showed metabolic acidosis at admission in both groups with no significant difference between the experimental and control groups (PH was 7.22 ± 0.08 versus 7.25± 0.05 respectively). Serum electrolytes (sodium, potassium and magnesium) were within normal range for both groups. Likewise, there were no significant differences between both groups regarding liver enzymes (SGOT and SGPT), kidney function (serum creatinine and blood urea), random blood sugar, total white blood cells (WBCs), platelets count. The levels of the cardiac marker troponin I were within normal reference range in both the experimental and control groups.

After 12 hours from admission, 11 patients in experimental group and 17 patients in control group were died.

Tables (6 and 7) demonstrate absence of any significant differences between both groups in the above investigations 12 hours after admission. There was an observed improvement in metabolic acidosis, but with no significant differences between the studied groups (PH was 7.35±0.11 versus 7.36±0.14 respectively). Moreover, troponin I levels were still within normal ranges in both groups at this time point.

Outcome of the studied groups:

Table (8) shows primary and secondary outcomes of the experimental and control groups as follow:

- The number of deaths in the experimental group was lower than the control group (56% versus 76% respectively), but it did not reach a significant level.
- The need for intubation and mechanical ventilation was significantly lower in the experimental group compared to the control group (36% versus 92 % respectively).
- The median duration of mechanical ventilation was non-significantly higher in the experimental group compared to the control group (24 hours vs 10 hours respectively).
- Total amount of norepinephrine administered by patients in the experimental group ranged from 12 - 32 mg. While, in the control group it was 8 -30 mg with no significant difference between both groups.
- The mean arterial blood pressure was assessed 12 hours after starting ILE infusion. Its mean was non-

significantly higher in the experimental group compared to the control group (50.31±9 versus 49.81±11.91 respectively).

- Patients in the experimental group showed a significantly longer stay in the hospital compared to those in the control group (a median length of hospital stay was 58 hours vs 12 hours respectively).

The survivors in the experimental and control groups were compared as regards the need for intubation and mechanical ventilation, and the length of hospital stay as demonstrated in table (9):

- Only one patient (9.1%) in the experimental group needed intubation and mechanical ventilation compared to four patients (66.7%) in the control group with a statistically significant difference.
- The median length of hospital stay was significantly lower in survivors of the experimental group compared to the control group (60 hours vs 98 hours respectively).

Likewise, **table (10)** illustrates a comparison between non- survivors in both groups

- All (100%) non-survivors in the control group need intubation and mechanical ventilation compared to only eight (57.1%) in the experimental group with a statistically significant difference.
- Non-survivors in the experimental group showed a significantly longer survival presented by higher median length of hospital stay compared to their counterparts in the control group (54 hours vs 12 hours respectively).

Assessment of ILE dosage and safety:

- The total amount of ILE received by patients in the experimental group ranged from 100 to 1000 ml with a median amount of 300 ml.
- In order to assess the safety of ILE, serum triglycerides, platelets count, and liver enzymes were compared at admission and 12h later during follow up of the experimental group as shown in table 8.

Serum triglyceride levels ranged from 37to 150 mg/dL at admission and from 40 to 150 mg/dl 12 hours after ILE administration with non- significant differences. Furthermore, the median platelets count and liver enzymes showed non -significant difference at admission and after 12 hours.

Table (1): Chi-Square test for Comparison of sociodemographic characteristics of the studied patients (N=50)

		Groups						Chi-Square test	
		Experimental (received ILE) N=25		Control (not received ILE) N=25		Total N=50			
		N	%	N	%	N	%	X^2	P value
Age groups (years)	<20	14	56	10	40	24	48	2.26	0.322
	20-30	3	12	7	28	10	20		
	>30-50	8	32	8	32	16	32		
Sex	Female	17	68	14	56	31	62	0.73	0.390
	Male	8	32	11	44	19	38		
Residence	Rural	21	84	20	80	41	82	0.00	1.00
	Urban	4	16	5	20	9	18		
Marital status	Single	16	64	13	52	29	58	0.73	0.390
	Married	9	36	12	48	21	42		
Education	Illiterate	2	8	2	8	4	8	0.53	0.902
	Primary	6	24	8	32	14	28		
	Secondary	17	68	15	60	32	64		
Occupation	Working	4	16	7	28	11	22	2.001	0.368
	Not working	9	36	5	20	14	28		
	Student	12	48	13	52	25	50		

n: number

Table (1): Mann-Whitney U test for Comparison of toxicological data of acute aluminum phosphide poisoning in the studied patients (N=50)

		Groups			Mann-Whitney U test	
		Experimental (received ILE) N=25	Control (not received ILE) N=25	Total N=50	Z_{mw}	P value
Amount (tablet)	Minimum – Maximum	0.25 -3	0.5 -3	0.25 -3	1.481	0.139
	Median	1	1	1		
	IQR	0.5-1	1-1	0.5-1		
	Mean rank	22.66	28.34			
Delay time (h)	Minimum – Maximum	1 – 6	1 - 5.5	1 - 6	-0.594	0.553
	Median	2	2	2		
	IQR	2-3	2-2	2-2		
	Mean rank	26.58	24.42			

N: number, IQR: Interquartile range.

Table (2): Chi-Square test for Comparison of clinical characteristics of the studied patients at the time of admission (N=50)

		Groups						Chi-Square test	
		Experimental (received ILE) N=25		Control (not received ILE) N=25		Total N=50			
		N	%	N	%	N	%	X^2	P value
Consciousness	Conscious	21	84	23	92	44	88	0.189	0.663
	Disturbed	4	16	2	8	6	12		
Blood pressure	Hypotension	15	60	17	68	32	64	0.347	0.556
	Undetected	10	40	8	32	18	36		
Oxygen Saturation	Normal	2	8	6	24	8	16	1.339	0.247
	Abnormal	23	92	19	76	42	84		
Pulse	Tachycardia	19	76	23	92	42	84	2.661	0.295
	Bradycardia	4	16	2	8	6	12		
	Undetected	2	8	0	0	2	4		
Respiratory rate	Normal	15	60	16	64	31	62	.085	0.771
	Tachypnea	10	40	9	36	19	38		
Temperature	Normal	19	76	21	84	40	80	0.500	0.480
	Hypothermia	6	24	4	16	10	20		
Chest	Free	15	60	16	64	31	62	0.805	0.837
	Dyspnea	6	24	7	28	13	26		
	Crepitation	4	16	2	8	6	12		
GIT	Vomiting	13	52	15	60	28	56	0.835	0.783
	Abdominal pain	4	16	2	8	6	12		
	Vomiting and abdominal pain	8	32	8	32	16	32		
ECG	Normal	11	44	13	52	24	48	0.321	0.571
	Abnormal	14	56	12	48	26	52		

N: number.

Table (3): Mann-Whitney U test and independent T test for Comparison of base line arterial blood gases, serum electrolytes levels and random blood sugar obtained at admission in the studied groups (N =50)

		Groups			Tests of significance	
		Experimental (received ILE) N=25	**Control (not received ILE) N=25**	**Total N=50**	**Test statistic**	**P value**
PH	Minimum- Maximum	7.10-7.35	7.15-7.35	7.10-7.35	t= -1.237	0.223
	Mean± SD	7.22 ± 0.08	7.25± 0.05	7.24±.07		
HCO_3	Minimum- Maximum	6-12	6.30-12	6-12	t= -0.360	0.720
	Mean± SD	7.54±1.66	7.69±1.39	7.61-1.52		
P_aCO_2	Minimum- Maximum	9 -43.60	9 -43.60	9±43.60	Z_{mw}= -1.217	0.224
	Median	19	14	18.90		
	IQR	18-31	13.60-25	13.60-30		
	Mean rank	28	23			
Serum sodium (mmol/L)	Minimum- Maximum	128.5-155	136-148	128.5-155	t= 0.132	0.895
	Mean± SD	142 ±8.24	141.76±3.76	141.88±6.34		
Serum potassium (mmol/L)	Minimum- Maximum	3.10-5.30	3.10-4.20	3.10-5.30	t= 1.465	0.149
	Mean± SD	3.78±0.55	3.58± 0.41	3.68±0.49		
Serum magnesium (mmol/L)	Minimum- Maximum	1.70-3.10	1.84-3	1.70-3.10	t= 1.654	0.106
	Mean± SD	2.28 ± 0.41	2.12 ±0.27	2.20 ± 0.35		
Random blood sugar (mg\L)	Minimum- Maximum	86-348	65-278	65-348	Z_{mw}= -0.787	0.432
	Median	151	128	129		
	IQR	123-171	103-196	113.00-196		
	Mean rank	27.12	23.88			

N: number, IQR: Interquartile range, SD: standard deviation, Zmw; Mann-Whitney U test, t; independent T test, RBS: Random blood sugar, PaCO2: partial pressure of carbon dioxide.

Table (4): Mann-Whitney U test for Comparison of base line serum troponin I level, liver enzymes, renal function tests and complete blood count obtained at admission in the studied groups (N=50).

		Groups			Mann-Whitney U test	
		Experimental (received ILE) N=25	**Control (not received ILE) N=25**	**Total N=50**	**Z_{mw}**	**P value**
Serum troponin I (ng/ml)	Minimum-Maximum	0.10-0.28	0.10-0.21	.10-.28	-0.491	0.623
	Median	0.13	0.12	0.13		
	IQR	0.12-0.15	0.12-0.14	0.12-0.15		
	Mean rank	26.5	24.5			
SGOT (U/L)	Minimum- Maximum	10-40	12-62	10-62	1.835	٠.067
	Median	19	26.00	21		
	IQR	17.5-31	19-41	18-40		
	Mean rank	21.74	29.26			
SGPT (U/L)	Minimum- Maximum	12-175	12-49	12-175	-0.924	0.356
	Median	22	18	22		
	IQR	15-40	13-41	15-41		
	Mean rank	27.4	23.6			
Blood urea (mg/dl)	Minimum- Maximum	17-51	17-48.9	17-51	0.849	0.396
	Median	28	31	31		
	IQR	27-35	28-37	27-37		
	Mean rank	23.76	27.24			
Serum creatinine (mg/dl)	Minimum- Maximum	0.5-1.9	0.7-1.9	0.50-1.9	1.657	0.098
	Median	0.92	1.28	0.96		
	IQR	0.70-1.02	0.84-1.33	0.80-1.33		
	Mean rank	22.1	28.9			
WBCs (mm^3)	Minimum- Maximum	3400-15000	3600-19600	3400-19600	0.645	0.519
	Median	8300	8900	8450		
	IQR	4300-11800	4300-11800	4300-11800		
	Mean rank	24.18	26.82			
Platelets (mm^3)	Minimum- Maximum	154000-280000	138000-394000	138000-394000	1.931	0.053
	Median	170000	204000	182000		
	IQR	165000- 184000	173000- 294000	165000- 244000		
	Mean rank	21.54	29.46			

N: number, IQR: Interquartile range, WBCs: white blood cells, SGOT; serum glutamic oxaloacetic transaminase, SGPT; serum glutamic pyruvic transaminase.

Table (5): Mann-Whitney U test and independent T test for Comparison of arterial blood gases, serum electrolytes levels and random blood sugar in the studied groups 12 hours after admission (N=22).

		Groups			Tests of significance	
		Experimental (received ILE) N=14	**Control (not received ILE) N=8**	**Total N=22**	**Test statistic**	**P value**
PH	Minimum-Maximum	7.03-7.45	7.22-7.65	7.03-7.65	t=-0.461	0.647
	Mean ±SD	7.35±0.11	7.36±0.14	7.35±0.12		
HCO_3	Minimum-Maximum	5.2- 25.5	9- 19.2	5.2- 25.5	Z_{mw}= -0.107	0.915
	Median	15	14	14.85		
	IQR	11.6- 16.1	12- 15.7	11.6- 16		
	Mean rank	25.72	25.28			
P_aCO_2	Minimum-Maximum	19- 41	23.5- 43	19- 43	Z_{mw}= -0.476	0.634
	Median	30	26.9	29.7		
	IQR	25-36.6	24.9-34	25-35		
	Mean rank	26.48	24.52			
Serum sodium (mmol\L)	Minimum-Maximum	134-155	138-152	134-155	t=-0.432	0.671
	Mean ±SD	141.14±6.67	142.38±6.00	141.59±6.31		
Serum potassium (mmol\L)	Minimum-Maximum	3.2-4.	3.2-4.2	3.2-4.2	t=-1.273	0.218
	Mean ±SD	3.66±0.24	3.83±0.35	3.72±0.29		
Serum magnesium (mmol\L)	Minimum-Maximum	1.7-2.3	2.06-2.1	1.70-2.3	t=-1.040	0.317
	Mean ±SD	2.03±0.2	2.09±0.02	2.05±0.16		
Random blood sugar (mg\L)	Minimum-Maximum	90-170	90-195	90-195	Z_{mw}= 0.472	0.482
	Median	121.50	132.50	124.00		
	IQR	100-140	95.5-165	100-150		
	Mean rank	10.75	12.81			

N: number, IQR: Interquartile range, SD: standard deviation, Zmw; Mann-Whitney U test, t; independent T test, RBS: Random blood sugar, PaCO2: partial pressure of carbon dioxide.

Table (6): Mann-Whitney U test and independent T test for Comparison of troponin I, liver enzymes and renal function after 12 hours of admission in the studied groups (N=22).

		Groups			Tests of significance	
		Experimental (received ILE) N=14	**Control (not received ILE) N=8**	**Total N=22**	**Test statistic**	**P value**
Serum troponin I (ng/ml)	Minimum-Maximum	0.11-0.16	0.11-0.16	0.11-0.16	t= -0.641	0.529
	Mean ± SD	0.13±0.02	0.14±0.02	0.13±0.02		
SGOT (U/L)	Minimum-Maximum	10-40	10-41	10-41	Z_{mw}= 0.731	0.764
	Median	18	23.5	18		
	IQR	16 -31	16-37.5	16-31		
	Mean rank	11.14	12.12			
SGPT (u/L)	Minimum-Maximum	12 -60	12-60	12-60	Z_{mw}= 0.810	0.815
	Median	20	18	20		
	IQR	15 -30	13.5-42.5	15-30		
	Mean rank	11.75	11.06			
Blood urea (mg/dl)	Minimum-Maximum	17 -51	17-51	17-51	Z_{mw}= 0.836	0.868
	Median	31	31	31		
	IQR	22- 49	29-41.5	27-49		
	Mean rank	11.29	11.88			
Serum creatinine (mg/dl)	Minimum-maximum	0.50-1.20	0.50-1.28	0.50-1.28	Z_{mw}= 0.891	0.920
	Median	0.92	0.90	0.91		
	IQR	0.70-1.20	0.72-1.15	0.70-1.20		
	Mean rank	11.36	11.75			
White blood cells	Minimum-maximum	3400-11800	4300-11800	3400-11800	Z_{mw}= 0.164	0.188
	Median	8200	4300	6950		
	IQR	4300 -8600	4300-6800	4300- 8300		
	Mean rank	12.93	9			
Platelets (mm^3)	Minimum-Maximum	150000-290000	150000-290000	150000-290000	t=0.269	0.790
	Mean± SD	202357.14± 41973.63	197125.00±47066.63	200454.55± 42844.93		

IQR: Interquartile range, SD: standard deviation, Zmw; Mann-Whitney U test, t; independent T test. WBCs: white blood cells, SGOT; serum glutamic oxaloacetic transaminase, SGPT; serum glutamic pyruvic transaminase.

Table (7): Mann-Whitney U test , independent T test and Chi-Square test for Comparison of primary and secondary outcomes of the studied patients in the experimental and control patients (N=50).

			Groups			Tests of significance	
			Experimental (received ILE) N=25	Control (not received ILE) N=25	Total N=50	Test statistic	P value
Mortality	Yes	N	14	19	33	X^2=2.228	0.136
		%	56	76	66		
	No	N	11	6	17		
		%	44	24	34		
Need of intubation and mechanical ventilation	Yes	N	9	23	32	X^2=17.014	<.001*
		%	36	92	64		
	No	N	16	2	18		
		%	64	8	36		
Duration of mechanical ventilation (hours)	Minimum-maximum		3-120	2-72	2-120	Z_{mw}=1.19	0.246
	Median		24	10	10		
	IQR		6-72	6-18	6-34		
	Mean rank		19.61	15.28			
Total amount of norepinephrine (mg)	Minimum-maximum		12-32	8-30	8-32	Z_{mw}=1.415	0.157
	Median		16	16	16		
	IQR		16-32	16-28	16-28		
	Mean rank		28.14	22.86			
Mean arterial blood pressure(mmHg) **	Minimum-Maximum		30-70	30-80	30-80	t=.149	0.882
	Mean± SD		50.31±9	49.81±11.91	50.08±10.30		
Length of hospital stay (hours)	Minimum-maximum		6-144	4-132	4-144	Z_{mw}=2.49	0.013*
	Median		58	12	48		
	IQR		48-72	9-48	11-72		
	Mean rank		30.64	20.36			

**significant at p< 0.05, IQR: Interquartile rang, SD: standard deviation, N: number, IQR: Interquartile range, Zmw; Mann-Whitney U test, t; independent T test, ** assessed 12 hours after ILE administration.*

Table (8): Mann-Whitney U test and Fisher's exact test for Comparison between survivors in the experimental and control groups as regards need of intubation/mechanical ventilation and length of hospital stay (N=17)

			Survivors			Tests of significance	
			Experimental (received ILE) N =11	Control (not received ILE) N=6	Total N=17	Test statistic	P value
Need of intubation and ventilation	Yes	N	1	4	5	Exact x^2 =4.08	0.028*
		%	9.1	66.7	29.4		
	No	N	10	2	12		
		%	90.9	33.3	70.6		
Duration of hospital stay (hours)	Minimum-maximum		48-84	72-132	48	Z_{mw}= 3.09	0.002*
	Median		60	98	72		
	IQR		54-72	96-120	58-96		
	Mean rank		6.23	14.08			

**significant at p< 0.05, IQR: Interquartile rang, N: number, Zmw; Mann-Whitney U test, X2FE: Fisher's exact test.*

Table (9): Mann-Whitney U test and Fisher's exact test for Comparison between non-survivors in the experimental and control groups as regards need of intubation/mechanical ventilation and length of hospital stay (N=33)

			Non-survivors				
			Experimental (received ILE) N=14	Control (not received ILE) N=19	Total N=33	Test statistic	P value
Need of intubation and ventilation	Yes	N	8	19	27	Exact x^2 = 7.28	0.003*
		%	57.1	100.0	81.8		
	No	N	6	0	6		
		%	42.9	0.0%	18.2		
Duration of hospital stay(hours)	Minimum-Maximum		6-144	4-48	4-144	Z_{mw}= 2.90	0.003*
	Median		54	12	12		
	IQR		11-96	8-14	9-50		
	Mean rank		22.68	121.82			

**significant at p< 0.05, IQR: Interquartile rang, Zmw; Mann-Whitney U test, X2FE: Fisher's exact test.*

Table (10): Wilcoxon signed rank test for Comparison of serum triglycerides, platelet count and liver enzymes at admission and after 12 hours of ILE administration in the experimental groups (N =14)

	Experimental group (received ILE) N=14			Wilcoxon signed rank test	
		At admission	After 12 h	Z	P value
Serum triglycerides (mg/dL)	Minimum- Maximum	37- 150	40 -150	-1.857	0.063
	Median	68	77.5		
	IQR	46 -99	55 -107		
	Mean rank	0.00	2.50		
Platelet count /C.mm)	Minimum- Maximum	154000-280000	150000-290000	-0.105	0.917
	Median	170000	187000		
	IQR	165000-184000	170000-244000		
	Mean rank	3.67	3.33		
SGOT(u/L)	Minimum- Maximum	10 – 40	10- 40	-0.743	0.458
	Median	19	18		
	IQR	17.5 – 31	16 - 31		
	Mean rank	3.5	1.5		
SGPT(u/L)	Minimum- Maximum	12- 175	12 - 175	-0.368	0.713
	Median	22	20		
	IQR	15 – 40	15 – 30		
	Mean rank	4	2		

IQR: Interquartile rang, SGOT; serum glutamic oxaloacetic transaminase, SGPT; serum glutamic pyruvic transaminase, N:number.

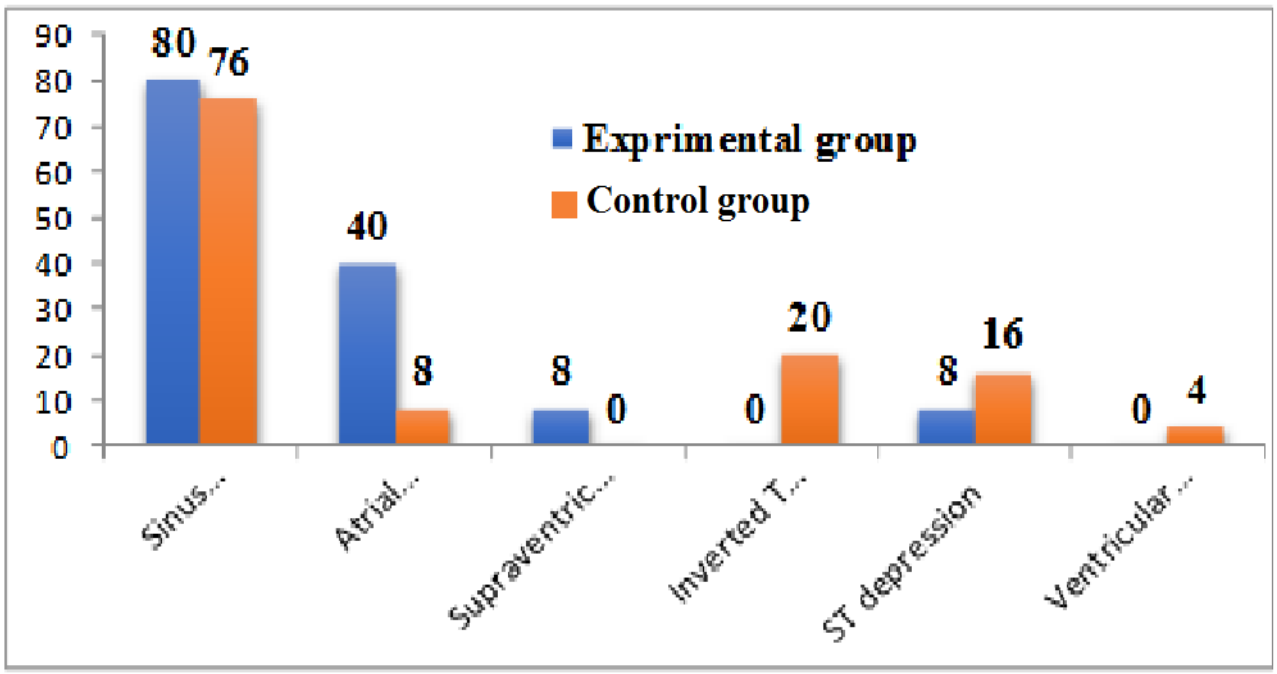

Fig. (1): ECG abnormalities in the experimental and control groups.

AF: Atrial fibrillation, SVT: Supraventricular tachycardia, VF: Ventricular fibrillation

Discussion

Aluminum phosphide is a well- known highly efficient rodenticide and insecticide. It is commonly used for protection of stored grains in Asian and African countries. Because of its wide availability and free accessibility, it is commonly used in suicide attempts in some countries such as Iran, India, Morocco and Egypt

(El-Naggar and El-Mahdy, 2011; Mostafalou et al., 2013).

The increased incidence of acute ALP poisoning and its high mortality is a real challenge for health professionals and emergency staff in the developing countries (Tehrani et al., 2013). Unfortunately, there is no specific antidote and the treatment is mainly supportive (Singh and Bhalla, 2015). Hence, evaluation of new treatment modalities is necessary, in order to decrease the rate of mortality and/or morbidity. Therefore, the aim of this study was to evaluate the efficacy and safety of intravenous lipid emulsion as an adjuvant therapy for acute ALP poisoning.

To the best of our knowledge, this study is the first randomized clinical trial that evaluated the efficacy and safety of ILE in ALP poisoning.

Diagnosis of ALP poisoning in this study has been done on the basis of patient history and suggestive clinical manifestations. Additionally, silver nitrate paper test has been done on gastric aspirate for biochemical detection of phosphine gas. But it was negative in all patients' gastric aspirate samples. This test is a simple and readily available bed side test. However, a false negative result may occur in patients being given oxygen. This might be due to conversion of phosphine to phosphorus pentoxide. Additionally, a false positive result may occur if there is hydrogen sulfide in the air (Chugh et al., 1991; Moghadamnia, 2012).

In this clinical trial, ILE administration reduced mortality rate of ALP poisoning to 56% compared to 76% in the control group. Though the observed improvement in survival of ALP poisoning did not reach a significant level, it could be considered a promising finding. In a previous two case reports; ILE administration had successfully resuscitated a severe case of ALP poisoning (Baruah et al., 2015).

It's known that ALP poisoning has high mortality rate ranged from 40%-91% within the first 24 hours (Alnasser et al., 2018). The presence of specific antidote which counteracts the toxicity and produces a significant reduction of this terrible rate of deaths is still not available (Singh and Bhalla, 2015). The main reason is that the exact mechanism of ALP toxicity is not yet clear and more studies are required to elucidate the exact mechanisms that may help to explore specific antidotes (Goharbari et al., 2018). Comparable to this finding, Taghaddosinejad et al. (2016) reported that ALP-poisoned patients that received N-acetylcysteine (NAC) infusion at 300 mg/kg for 20 hours showed an improved hemodynamic status. Nevertheless, the mortality rate was non-significantly reduced to 30.4% compared to 43.5% in the control group. The observed lower rate of mortality in their study is attributed to exclusion of cases died in the first 24 hours after admission to hospital. Likewise, Tehrani et al.(2013) detected non-significant reduction in mortality rate of ALP poisoned patients with NAC treatment (mortality rate in NAC treatment and control groups were 36% and 60%, respectively), and concluded that NAC may have a therapeutic effect in acute aluminum phosphide poisoning. Recently, Goharbari et al. (2018) examined the usefulness of 50 mg liothyronine administration via nasogastric tube after gastric lavage, in the first 6 h of ALP poisoning. They also identified non-significant improvement in the mortality rate (25% versus 33.3% in the experimental and control groups respectively).

Intravenous lipid emulsion is a proven resuscitative therapy in severe refractory cases of systemic local anesthetic drugs toxicity (Picard et al., 2014; Weinberg, 2010). Additionally, it has been shown that unstable hemodynamics of patients with overdose of non-local anesthetic drugs with lipophilic properties such as beta blockers, calcium channel blockers, tricyclic antidepressants, and some psychotropic agents respond to the administration of ILE (Rothschild et al., 2010). Moreover, a randomized clinical trial used a continuous infusion of 10% ILE has detected an improvement in Glasgow coma scale 6 hours after acute poisoning with various medications including benzodiazepines, tricyclic antidepressants, anticonvulsants, anticholinergics, antihistamines, muscle relaxants, selective serotonin reuptake inhibitors, antipsychotics, acetaminophen, salicylates, and opioids (Taftachi et al., 2012). Thus, ILE could be considered as a universal antidote for various types of acute poisoning.

Unfortunately, supportive management such as gastrointestinal lavage, intravenous infusion of crystalloids, bicarbonate, calcium gluconate, magnesium sulfate, vasopressors, albumin and oxygen therapy usually fail to restore cardiac systolic function and to resolve the patient's severe hypotension. So, they are not sufficient to improve survival (Agrawal et al., 2015). This explain the reported high mortality (76%) in the control group that only received the standard conventional treatment.

It has been reported that the main cause of death in ALP poisoning is cardiogenic shock which is presented by profound hypotension not responsive to conventional treatment (Mehrpour et al., 2012;Karami-Mohajeri et al., 2013). The exact mechanism for refractory cardiogenic shock is not known. It may be occurring due to dysrhythmias, electric conduction disturbance, and toxic myocardial damage (Karami-Mohajeri et al., 2013). At cellular level, the main mechanism is an inhibition of cytochrome c oxidase in the cardiomyocyte mitochondria, resulting in a decreased ATP production, oxidative stress and cardiomyocytes death (Abdolghaffari et al., 2015). Furthermore, a decrease in fatty acid oxidation after myocardial hypoxia leads to accumulation of long-chain acyl-CoA esters, which inhibits adenine nucleotide translocation, with a net result that lowers the energy charge of the cell, adversely affecting muscle contraction and electrical conduction (Noordali et al., 2017).

In this regard, the clinical findings in the present study showed that 64% of patients presented with

hypotension while the blood pressure was undetected in the remaining ones. Furthermore, assessment of the mean arterial blood pressure 12 hours after ILE administration revealed non-significant increase in the experimental group compared to the control group (50.31±9 versus 49.81±11.91 respectively). This means that ILE could not able to maintain blood pressure in the higher range and it was not significantly effective to control the cardiogenic shock. Thus, the total amount of the administered norepinephrine was non-significantly different in the two studied groups.

In the present study, troponin I level as a biochemical marker of cardiac muscle injury was analyzed both at admission and after 12 hours. At these two time points, the median levels of troponin I were within normal reference ranges, with no significant difference between both groups. Despite the observed ECG changes in most cases of acute ALP poisoning, inconsistent reports of normal and abnormal cardiac markers levels were found (Soltaninejad et al., 2009). Some case reports of ALP poisoning documented myocardial injury by elevation in the cardiac markers creatin phosphokinase-myocardial band (CPK-MB) and troponin levels (Elabbassi et al., 2014; Shah et al., 2009). However, other reports showed normal serum levels of cardiac markers at admission (Nayyar and Nair, 2009). Moreover, Karami-Mohajeri et al.(2013) concluded that the normal levels of cardiac markers cannot disprove cardiotoxicity though their elevated levels can verify myocardial damage. It seems that, levels of cardiac markers are related to time passed since toxic exposure. Repeated measures of CPK and CPK-MB levels at 0, 12, 18, and 24 h after admission revealed progressive elevation, with significant differences between the mean levels at the studied time points (Taghaddosinejad et al., 2016). Further serial troponin I level measurements are recommended to show any significant differences between the experimental and control groups.

Previous studies on local anesthetic drugs toxicity proposed that ILE infusion improved mitochondrial function by providing a source of intracellular fatty acids, thereby overcoming the reduction in the ATP production especially in cardiomyocytes (Haworth and Smart, 2012). Added to that, it increases the intra myocyte calcium level leading to a direct positive inotropic effect (Kuo and Odunayo, 2013). Further, visual demonstration of the lipid sink effect of ILE in cases of bupivacaine and lidocaine has been provided. Despite these beneficial effects, ILE infusion in this study did not show complete therapeutic effects on blood pressure as mentioned above. The possible reason underlying the suboptimal efficacy of ILE is the increased demand of ATP as a result of its positive inotropic effect, which may finally lead to ATP depletion (Papadopoulou et al., 2012). Further assessment of cardiomyocytes mitochondrial dysfunction and oxidative stress with ILE infusion in ALP poisoned patients is warranted. Furthermore, the dose of ILE might be insufficient to produce effective restoration of cardiac function and the blood pressure.

According to Baruah et al. (2015), the used regimen in this study was ILE 20% at a rate of 10 ml/h that gradually tapered with monitoring of serum triglyceride level. The total amount of ILE received by patients in the experimental group ranged from 100 to 1000 ml with a median amount of 300 ml. Actually, the optimum dose of ILE in acute intoxication is not clear except in local anesthetic toxicity (Aggarwal et al., 2018). The Current guidelines of the American Society of Regional Anesthesia (ASRA) and the Association of Anaesthetists of Great Britain and Ireland (AAGBI) recommended ILE Therapy (20%) as a bolus of 1.5 mL/kg over 1 min followed by continuous infusion of 0.25 mL/kg/min with upper limit of 10 mL/kg over the first 30 mins (Neal et al., 2018). But for safety concerns, the used regimen in our study was based on the ILE doses that were previously used for resuscitation of cases of ALP poisoning (Baruah et al., 2015). Further assessment of other ILE regimens to explore more about its efficacy and safety is highly needed.

Becker and Young (2017) reported that ILE is an overall safe therapy that should be considered for a variety of toxicities that cause neurologic or cardiovascular instability. Despite this, the safety of acute, high-volume lipid emulsion infusion is not precisely known (Weinberg, 2010). Some complications such as allergic reactions, lipemia, elevated liver enzymes, thrombocytopenia, and hyperthermia are the anticipated side-effects that are satisfactorily responsive to supportive treatments (Cave et al., 2011). Fortunately, in this study, follow up of serum triglycerides levels, platelets count, and liver enzymes at admission and 12 hours later showed no abnormalities with no significant differences. This agree with Weinberg (2017) who stated that no side effect have been recorded in lipid-based resuscitations and no serious clinical complications have been reported following use of lipid emulsion for treating drug-induced toxicity.

A key finding in the present study was the significant reduction in the need for intubation and mechanical ventilation in patients received ILE infusion (36% versus 92 % in the experimental and control groups respectively).

Intensive care admission for the need of mechanical ventilation is frequently required in ALP poisoning due to hypoxia, adult respiratory distress syndrome, and disturbed conscious level (Abd Elghany et al. 2018; Louriz et al. 2009; Mehrpour et al. 2008). Definitely, the favorable effects of ILE in this regard minimize costs, efforts, and the complications related to ventilation.

The present work also revealed another favorable effect of ILE administration on the hospital stay. The median length of hospital stay was significantly lower in survivors of the experimental group compared to the control group (60 hours vs 98

hours respectively). This is in accordance with Weinberg, (2012) who stated that intubation and duration of intensive care units stay in patients with multi- drug over dose such as (benzodiazepines, Tricyclic antidepressants, other antidepressants anticonvulsants, beta blockers and calcium channel blockers) who received lipid emulsion was found to be shorter than matched controls.

Non- survivors of the experimental group showed longer survival time with a median hospital stay of 54 hours compared to 12 hours in the control group. This longer hospital stay could be related to the longer duration of mechanical ventilation recorded in the experimental group.

Unfortunately, it was observed that most of the non- survivors in the experimental group were kept stabilized but, inappropriately for unknown mechanisms they suddenly deteriorated and developed cardiac arrest.

Conclusion

It could be concluded that, administration of ILE 20% in acute ALP poisoning at a rate of 10ml/h IV infusion is an overall safe therapy. Furthermore, ILE use in this study has significantly reduced the need for intubation and mechanical ventilation. But it did not decrease the mortality rate to a significant level. Thus, the adjuvant ILE use along with the conventional supportive treatment could have a therapeutic effect in ALP poisoned patients. Further multicenter randomized controlled trials for evaluation of the efficacy and safety of different ILE regimens is highly recommended. In addition, further serial troponin I level measurements are recommended to show any possible cardioprotective effects of ILE.

Recommendation

Further multicenter randomized controlled trials for evaluation of the efficacy and safety of different ILE regimens is highly recommended.

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الملخص العربى

تقييم مستحلب الدهون الوريدي كعلاج مساعد في التسمم الحاد بفوسفيد الألومنيوم: تجربة عشوائية منضبطة

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المقدمة :

فوسفيد الألومنيوم هو مبيد حشرى ذو فعالية عالية. وتعد الزيادة في معدل حالات التسمم الحاد بفوسفيد الألومنيوم وارتفاع معدلات الوفيات به بمثابه تحدى حقيقي للعاملين فى مجال الرعاية الصحية خاصه فى البلدان النامية .ويعتمد علاج هذه الحالات بشكل رئيسي على الرعاية الأساسية للمريض لعدم وجود ترياق محدد له حاليا . وبالتالي ، لذلك فإن تقييم طرق علاج جديدة أمر ضروري ، من أجل خفض معدل الوفيات.

الهدف من هذه الدراسة:

لذلك ، كان الهدف من هذه الدراسة هو تقييم فعالية وأمان مستحلب الدهون عن طريق الوريد كعلاج مساعد فى حالات التسمم الحاد بفوسفيد الالمونيوم.

المرضى وطرق البحث:

تم إجراء هذه الدراسة على خمسين مريضًا يعانون من التسمم الحاد بفوسفيد الالمونيوم وتم اختيار المشاركين في الدراسة من وحدة علاج التسمم بمستشفى الطوارئ بجامعة طنطا، خلال الفترة من بداية ديسمبر ٢٠١٦ وحتى نوفمبر ٢٠١٧.وتم توزيع المشاركين في الدراسة بشكل عشوائي على مجموعتين متساويتين (٢٥ مريضًا) لكل منهما: وقد اعطيت المجموعة التجريبية مستحلب الدهون ٢٠٪ بالتنقيط الوريدى بمعدل ١٠مل / ساعة ثم سحبها تدريجيا بالإضافة إلى العلاج المعتاد فى مثل هذه الحالات وتلقت المجموعة الضابطة العلاج التقليدي فقط.

النتائج:

كان عدد الوفيات في المجموعة التجريبية أقل من المجموعة الضابطة (٥٦ ٪ مقابل ٧٦ ٪ على التوالي)، لكنها لم تصل إلى مستوى ذو دلاله إحصائية. كانت الحاجة إلى تركيب الانبوبة الحنجرية والتنفس الصناعى أقل بدلالة إحصائية في المجموعة التجريبية مقارنة بالمجموعة ضابطة (٣٦٪ مقابل ٩٢٪ على التوالي). وكان متوسط مدة الاقامة فى المستشفى أقل لدى الأحياء في المجموعة التجريبية مقارنةً بالمجموعة الضابطة(٦٠ ساعة مقابل ٩٨ ساعة على التوالي).

الاستنتاج:

ومن ثم يمكن أن نستنتج أن إعطاء ٢٠٪ من مستحلب الدهون الوريدى في حالات التسمم الحاد بفوسفيد الالمونيوم بمعدل ١٠ مل / ساعة من التنقيط الوريدي هو علاج آمن بشكل عام. علاوة على ذلك ، فإن استخدام مستحلب الدهون الوريدى كعلاج مساعد مع العلاج التقليدي يمكن أن يكون له تأثير علاجي فعال في مثل هذه الحالات .

[1] قسم الطب الشرعي والسموم الإكلينيكي، كلية الطب، جامعة طنطا، مصر