Early L-carnitine Therapy in Severe Acute Aluminum Phosphide Poisoning: A Randomized Controlled Clinical Trial

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ABSTRACT

Introduction: Aluminum phosphide (AlP) is a common solid fumigant pesticide used for agricultural and nonagricultural purposes. In Egypt, AlP tablets are frequently used to commit suicide, and AlP poisoning constituting a frequent cause of admission and mortality in poison control centers. Current management of AlP poisoning is limited to supportive care; as there is no specific antidote. **Objectives:** to evaluate the therapeutic effect and safety of early L-carnitine administration, as an antioxidant, in treatment of severe acute AlP poisoning. **Material and methods:** This study was a randomized controlled clinical trial. It was conducted in Tanta Poison Control center (Emergency Hospital, Tanta University). Fifty acute AlP intoxicated patients were randomly allocated into two equal groups A and B using the sequentially numbered, opaque sealed envelopes method. Group A received only the routine treatment. Group B received L – Carnitine therapy as follow: 9 ampoules (9 gm) of L- Carnitine in 500 ml of 0.9% normal saline given as continuous IV infusion, until improvement or death in addition to the routine treatment. Complete physical examination, routine laboratory investigations and oxidative stress markers; malondialdehyde (MDA), total antioxidant capacity (TAC) and reduced glutathione (GSH) were assessed for each patient. **Results:** Comparison between groups A and B 12 hrs after admission revealed significant reduction of the mean MDA levels in group B than group A (7.54± 1.74 and 16.22± 2.95 respectively, $p<0.001$). At the same time, group B showed significant elevation in the mean TAC (5.70±1.55 and 12.88±2.49 respectively) and GSH levels (2.37±.89, 4.09±.86 respectively). Additionally, the need for intubation and mechanical ventilation was significantly lower in group B compared to group A (20% versus 56 % respectively). However, there was non-significant reduction in the number of deaths in patients on L-carnitine therapy (group B) compared with group A (60% and 80% respectively, $p >0.05$). **Conclusion:** Early administration of L-carnitine IV infusion was effective and safe as an adjuvant treatment of AlP poisoned patients.

Keywords: aluminum phosphide; L-carnitine; oxidative stress; malondialdehyde; reduced glutathione; total antioxidant capacity.

INTRODUCTION:

Aluminium phosphide (AlP) is a solid fumigant pesticide. It is extensively used in developing countries as a grain preservative. The common use of AlP tablets is due to their low cost, high efficiency, and wide availability **(Farahani et al., 2016).**

In Egypt, AlP tablets are frequently used to commit suicide especially among teenagers, and AlP poisoning constituting a frequent cause of admission to poison control centers **(Badawi et al., 2018).** Globally, the annual death rate due to pesticide poisoning is about 300,000. Many of these deaths ensuing from AlP Poisoning. The Mortality rate of AlP poisoning is characteristically high. It may reach 100% in some poison control centers. Outcome depends on the ingested amount, whether the tablet is fresh or expired, and the time interval between exposure and starting supportive care **(Hashemi-Domeneh et al., 2016).** Patients mostly die due to cardiovascular collapse, refractory shock, severe acidemia, fulminant hepatic failure, and/or adult respiratory distress syndrome **(Navabi et al., 2018).** Aluminium phosphide poisoning is typically rapidly progressive. Great numbers of deaths occur in the first 24 hrs, and in severe cases death can occur as early as 3 hrs following toxic exposure. **(Farahani et al., 2016).**

Following AlP ingestion, it reacts with water and hydrochloric acid in the stomach liberating phosphine (PH3) gas which is absorbed through the gastric mucosa **(Navabi et al., 2018).** At cellular level, phosphine causes disruption of mitochondrial function. It mostly inhibits cytochrome c oxidase activity (Complex IV) besides disruption of Complex I and Complex II chains. Finally, ATP formation is highly diminished **(Sciuto et al., 2016).**

Furthermore, it has been reported that PH3 leads to enhanced production of reactive oxygen species (ROS) and induces oxidative stress through inhibition of enzymatic antioxidants e.g. catalase (CAT), glutathione, glutathione reductase (GR) and superoxide dismutase (SOD). These alterations accelerates lipid peroxidation which result in damage of cell membrane, disruption of ionic barriers, nucleic acid damage, and finally cell death **(Gouda et al., 2018).**

Current management of AlP poisoning is limited to supportive care; as there is no specific antidote has been determined so far **(Dorooshi et al., 2018).**

Thus, it is essential to develop beneficial therapeutic interventions based on the proposed mechanisms of phosphine poisoning **(Sciuto et al., 2016).** As most severe cases presents early by cardiovascular collapse, drugs which work at the mitochondrial level to improve the metabolism of cardiac muscle cells may be a useful aide **(Elabbassi et al., 2014).**

Successful resuscitation of severe AlP poisoning using aggressive hemodynamic support and L-carnitine has been reported**(Elabbassi et al., 2014).** Additionally, addition of L-carnitine therapy to steroids and magnesium sulfate has rescued a case of severe AlP poisoning with an observed rapid reversal of myocardial cell dysfunction **(Sumit and Vishnu, 2015).**

Considering these favorable reports, the aim of the present study was to evaluate the therapeutic effect and safety of early L-carnitine

administration, as an antioxidant, in treatment of severe acute AlP poisoning.

MATERIALS& METHODS

Study design, setting and ethical considerations:

This study was a randomized controlled, parallel-group, phase II clinical trial (RCT). The study participants were recruited from Tanta Poison Control center, Emergency Hospital, Tanta University starting from June 2018 till the end of May, 2019. 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.

Sample size:

Sample size was calculated by G power 3.1.9.4 software program depending on the primary outcome. The minimum required sample size per group was 25 according to these assumptions; p1=0.8, p2=0.4, 5% margin of error, power of 80%, allocation ratio 1:1, and at two-sided hypothesis.

Eligibility criteria:

Inclusion criteria:

Patients aged 12 years or older of either sex, presented early within 3 hrs of toxic exposure, with severe symptomatic acute AlP poisoning: Defined by the presence of hemodynamic compromise in the form of systolic blood pressure <90 at the time of presentation.

Diagnosis was based on history of exposure including reliable identification of the compound based on the container brought by patient's relatives, suggestive clinical manifestations following shortly a single exposure to AlP tablets, and biochemical detection of phosphine gas in gastric aspirate by silver nitrate test **(Chugh et al., 1989).**

Exclusion criteria:

Asymptomatic patients with history of acute aluminum phosphide exposure, co ingestion or exposure to other substances, presence of major medical conditions (e.g. cardiovascular disease, renal or hepatic failure). In addition, patients presented more than 3 hours of having ingested AlP tablets or received treatment for acute AlP poisoning in any medical center before admission. Pregnant and lactating women were also excluded from the study.

Methods:

Fifty patients were randomly allocated into control (A) and intervention (B) groups (25patients each) by means of the serially numbered, opaque wrapped envelopes method **(Doig et al., 2005).**

Group A:

Patients in this group received only the standard treatment of AlP poisoning including care for airway, breathing and

circulation. Intravenous fluids guided by central venous pressure measurement and vasopressors (Norepinephrine) IV infusion has been used to treat hypotension and refractory shock. Correction of metabolic acidosis by intravenous sodium bicarbonate was also considered. Additionally, magnesium sulfate: 1g IV infusion every 1hr for the first 3 hrs, followed by 1–1.5 g every 6 hrs for 24 hrs was administered. Decontamination was done by gastric lavage using normal saline mixed with sodium bicarbonate solution (2 ampoules sodium bicarbonate 25% added to each 500cc saline) in all Patients presented within 2 hrs of toxic ingestion. Then, a single (50 gm) dose of activated charcoal was administered **(Farahani et al., 2016).**

Group B:

In addition to the conventional treatment described above, patients in this group received L – Carnitine therapy as follow: 9 ampoules (9 gm) of L carnitine added in 500 ml of 0.9% normal saline and given as continuous IV infusion, until improvement or death **(Sumit and Vishnu, 2015).**

The study participants of both groups were subjected to full history taking including age, gender, circumstances of poisoning whether intentional or accidental, amount and route of exposure, time interval between exposure and starting treatment, and history of medical diseases such as liver, renal or cardiac diseases. Additionally, thorough physical examination including vital signs, assessment of level of consciousness by Glasgow coma scale, cardiovascular examination including Electrocardiography (ECG), chest and abdominal examination were done. Immediately after admission and before starting treatment, arterial and venous blood samples were obtained for blood gas analysis and for assessment of the biochemical profile and some oxidative stress biomarkers. These included malondialdehyde (MDA) **(Ohkawa et al., 1979)**, Total antioxidant capacity (TAC)**(Koracevic et al., 2001)**, and reduced glutathione (GSH)**(Tietze, 1969)** levels . Another venous blood sample was withdrawn to reassess the oxidative stress biomarkers 12 hrs after admission.

All participating patients were prospectively observed until discharge from the hospital or death. Regular measurement and recording of their vital signs, oxygen saturation, and conscious level were done. Occurrence of any adverse effect to drug therapy was documented.

Outcome measures:

The primary outcome was mortality whereas, ssssecondary outcome measures included the need foiintubation and mechanical ventilation, the recreceived total dose of norepinephrine which was assassessed at the time of discharge, and the length of hospital stay.

Statistics:

Data were tabulated and analyzed using Statistical Package for the Social Sciences (SPSS) for Windows, version 22.0 (SPSS, Chicago, IL, USA). Shapiro-Wilk test for normality was performed to investigate distribution of quantitative data. 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, paired T test was used to compare oxidative stress biomarkers within each group. Moreover, experimental event rate (EVR) which is the proportion of cases in the intervention group that had the outcome of interest, and absolute risk reduction (ARR) which is the proportion experiencing the event in control group minus the proportion experiencing the event in intervention group were calculated for dichotomous outcome variables. Significance was adopted at $p < 0.05$ for interpretation of results of tests.

RESULTS

Table (1) shows baseline demographic, toxicity and clinical characteristics of the study groups at the time of admission. Groups A and B were homogenous with no significant differences concerning age and gender ($p>0.05$). All (100%) patients assumed suicidal ingestion of AlP tablets. The median ingested toxic dose was 1 tablet in both groups, and the median duration between toxic exposure and arrival to hospital was 2 and 1.5 hrs respectively with no significant differences between groups A and B($p>0.05$). In addition, distribution of clinical manifestations including consciousness level, vital signs, presence of vomiting and abdominal pain, and ECG evaluation at the time of admission was comparable in both groups ($p>0$ .05).

Comparison of the routine laboratory investigations of the two studied groups including liver enzymes (ALT and AST)**,** serum creatinine, Blood urea, serum sodium (Na), serum potassium (K), PH, P_aCO_2, HCO_3, and O_2 saturation demonstrated statistically insignificant difference ($p>0.05$) as shown in table (2).

Table (3) demonstrates absence of statistically significant differences between groups A and B in mean plasma levels of MDA, TAC, and reduced glutathione (GSH) at the time of admission ($p>0.05$). Comparison between groups A and B 12 hrs after admission revealed significant reduction of the mean MDA levels in group B than group A (7.54± 1.74 and 16.22± 2.95 respectively, $p<0.001$). At the same time, group B showed significant elevation in the mean TAC (5.70±1.55 and 12.88±2.49 respectively) and GSH levels (2.37±.89, 4.09±.86 respectively). Within group A, comparison of each of the oxidative stress biomarkers at admission and 12 hrs later revealed progressive oxidative stress represented by significant increase in the mean MDA levels (13.9± 3.0, 16.22±2.95 respectively, $p<.001$). On the other hand, patients received L-carnitine in group B displayed improvement in the form of significant reduction in the mean MDA levels associated with significant elevation in the mean TAC, and GSH levels ($p<0.001$).

Primary and secondary outcomes of the studied groups were illustrated in table (4). There was non-significant reduction in the number of deaths in patients on L-carnitine therapy (group B) compared with group A (60% and 80%

respectively, p >0.05, ARR=20%). Whereas, the need for intubation and mechanical ventilation was significantly lower in group B compared to group A (20% versus 56 % respectively, ARR= 36% and 95% CI=11.01%-60.99%). The median total amount of norepinephrine administered by patients in groups A and B were comparable with no significant difference between both groups (p=.296) .Concerning the length of hospital stay, patients received L carnitine in group B required a significantly longer duration compared to patients received standard supportive care in group A (the median length of hospital stay was 36 hrs vs 14 hrs respectively, p=.028).

Survivors of group B showed significantly lower median duration of hospital stay compared to group A (44 hrs vs 99 hrs respectively, p=.001) (Table 5). In addition, comparison of non-survivors in both groups revealed a statistically significant reduction in the rate of intubation and mechanical ventilation in patients of group B (26.7% vs 65.0% respectively, ARR= 38.33%, CI=7.71%-68.96%), but these patients (group B) needed a significantly longer duration of hospital stay (median stay was 23 hrs vs 12 hrs respectively) (Table 6).

Silver nitrate test was done to confirm diagnosis and it was positive in all (100%) the studied patients. Additionally, meticulous follow up of patients received L-carnitine therapy (Group B) did not show any major adverse effects in comparison with patients received only the standard management (Group A).

Table (1): Base line demographic, toxicity, clinical, and ECG characteristics of the study groups (n=50)

		Groups				Tests of significance	
		Supportive A (n=25)		Intervention B (n=25)		Test statistic	P value
Age (Years)	Mean ± SD	23.9±7.6		22.9±7.8		.422	.66
Sex N (%)	Female	14	56.0 %	15	60.0%	.082	.774
	Male	11	44.0 %	10	40.0%		
Toxic dose (tablet)	Median (IQR)	1.0 (1.0-1.0)		1.0 (0.5-1.0)		.126	.899
Duration between exposure and arrival to hospital (h)	Median (IQR)	2.0 (2.0-2.0)		1.50 (1.0-2.0)		1.850	.064
Consciousness	Conscious	20	80.0	19	76.0	.117	.73

N (%)	Disturbed	5	20.0	6	24.0		3
Blood pressure	Hypotension	18	72.0	21	84.0	1.049	.30
N (%)	Undetected	7	28.0	4	16.0		6
Pulse	Normal	8	32.0	8	32.0	.366	.83
N (%)	Tachycardia	15	60.0	16	64.0		3
	Undetected	2	8.0	1	4.0		
Respiratory rate	Normal	7	28.0	11	44.0	1.389	.23
N (%)	Tachypnea	18	72.0	14	56.0		9
Temperature	Hypothermia	4	16.0	2	8.0	.189	.66
N (%)	Normal	21	84.0	23	92.0		7
Vomiting	No	16	64.0	17	68.0	.089	.76
N (%)	Yes	9	36.0	8	32.0		5
Abdominal pain	No	21	84.0	23	92.0	.771	.66
N (%)	Yes	4	16.0	2	8.0		7
ECG	Normal	2	8.0	1	4.0	4.308	.83
N (%)	Sinus Tachycardia	13	52.0	15	60.0		7
	Sinus Brady.	2	8.0	1	4.0		
	AF	1	4.0	2	8.0		
	Extrasystole	1	4.0	3	12.0		
	Inverted T-wave	2	8.0	2	8.0		
	S-T elevation	3	12.0	1	4.0		
	Ventricular tachycardia	1	4.0	0	0.0		

P: p value for comparing between the studied groups *: Statistically significant at $p < 0.05$

Table (2): Base line laboratory characteristics of the study groups (n=50)

		Groups		Independent samples T test	
		Supportive A (n=25)	Intervention B (n=25)	t	P value
ALT	Minimum	10.0	7.0	.310	.758
	Maximum	40.0	29.0		
	Mean	19.9	19.3		
	SD	7.6	6.0		
AST	Minimum	14.0	10.0	1.058	.071
	Maximum	30.0	40.0		

	Mean	19.4	22.4		
	SD	3.6	7.3		
Serum creatinine	Minimum	.5	.5	.212	.833
	Maximum	1.2	1.2		
	Mean	.8	.8		
	SD	.2	.2		
Blood urea	Minimum	15.0	18.0	1.41	.164
	Maximum	40.0	40.0		
	Mean	22.1	24.4		
	SD	5.8	5.6		
Serum sodium	Minimum	135.5	133.0	.166	.869
	Maximum	147.0	149.0		
	Mean	140.4	140.2		
	SD	3.4	4.7		
Serum potassium	Minimum	3.0	2.9	1.48	.143
	Maximum	4.5	4.6		
	Mean	3.9	3.7		
	SD	.4	.4		
PH	Minimum	7.10	7.10	.445	.658
	Maximum	7.50	7.40		
	Mean	7.21	7.23		
	SD	.09	.10		
P_aCO2	Minimum	14.0	19.0	1.90	.064
	Maximum	44.0	44.0		
	Mean	30.7	35.0		
	SD	9.4	6.1		
Oxygen saturation	Minimum	70.0	70.0	.846	.402
	Maximum	99.0	99.0		
	Mean	87.8	89.8		
	SD	8.1	7.9		
HCO3	Minimum	6.3	8.5	1.52	.134
	Maximum	26.0	24.0		
	Mean	13.9	16.2		
	SD	5.5	5.1		

P: p value for comparing between the studied groups
*: Statistically significant at $p < 0.05$

Table (3): Evaluation of plasma malondialdehyde, total antioxidant capacity, and reduced glutathione levels in the two studied groups at admission and 12 hrs later

		Groups		Independent samples T test	
		Supportive (A)	Intervention (B)	t	P value
Plasma MDA (nmol/ml) At admission	Minimum	10.5	10.2	1.01	.313
	Maximum	20.4	20.2		
	Mean	13.9	14.8		
	SD	3.0	3.3		
Plasma MDA (nmol/ml) 12 hrs after admission	Minimum	12.00	4.00	11.01	<.001*
	Maximum	22.10	10.51		
	Mean	16.22	7.54		
	SD	2.95	1.74		
Paired T test	t	5.89	15.31		
	P value	<.001*	<.001*		
Plasma TAC (mM/L) At admission	Minimum	3.5	2.5	.580	.564
	Maximum	8.9	9.0		
	Mean	5.3	5.1		
	SD	1.5	1.4		
Plasma TAC (mM/L) 12 hrs after admission	Minimum	3.50	10.00	10.64	<.001*
	Maximum	8.90	18.00		
	Mean	5.70	12.88		
	SD	1.55	2.49		
Paired T test	t	1.72	13.73		
	P value	.103	<.001*		
GSH (mmol/ml) At admission	Minimum	1.00	.16	.049	.961
	Maximum	3.50	3.50		
	Mean	2.15	2.16		
	SD	.69	.80		
GSH (mmol/ml) 12 hrs after	Minimum	1.00	2.90	6.24	<.001*
	Maximum	4.10	6.00		
	Mean	2.37	4.09		

admission	SD	.89	.86		
Paired T test	t	1.096	13.32		
	P value	.066	<.001*		

MDA: malondialdehyde, TAC: total antioxidant capacity, GSH: reduced glutathione
P: p value for comparing between the studied groups
*: Statistically significant at $p < 0.05$

Table (4): Comparison of primary and secondary outcomes in the studied groups (n=50)

			Groups				Magnitude of the effect	
			Supportive A (n=25)	Intervention B (n=25)	Test statistic	P value	EVR	ARR (95% CI)
Mortality	Died	N	20	15	2.381	.123	60 %	20% (-4.79%-44.79%)
		%	80.0	60.0				
	Survived	N	5	10				
		%	20.0	40.0				
Need for intubation and mechanical ventilation	No	N	11	20	6.876	.009*		
		%	44.0	80.0				
	Yes	N	14	5			20%	36% (11.01%-60.99%)
		%	56.0	20.0				
Amount of norepinephrine (mg)	Minimum		7.0	10.0	1.045	.296	Not applicable	
	Maximum		72.0	88.0				

	Median	32.0	32.0			
	IQR	10.0-40.0	16.0-45.0			
	Mean rank	23.36	27.64			
Hospital stay (hrs)	Minimum	4.0	2.0	2.196	.028*	Not applicable
	Maximum	144.0	168.0			
	Median	14.0	36.0			
	IQR	10.0-24.0	18.0-48.0			
	Mean rank	20.98	30.02			

P: p value for comparing between the studied groups
*: Statistically significant at $p < 0.05$
EVR: Experiment event rate
ARR: Absolute risk reduction
CI: confidence interval.

Table (5): Comparison between survivors in the studied groups as regards need of mechanical ventilation and length of hospital stay (n= 15).

Survivors			Groups		Tests of significance	
			Supportive n=5	Intervention n=10	Test statistic	P value
Need for intubation and mechanical ventilation	No	N	4	9	.288	.591
		%	80.0	90.0		
	Yes	N	1	1		
		%	20.0	10.0		
Hospital stay (hrs)	Minimum		60.0	24.0	3.017	.001*
	Maximum		144.0	60.0		
	Median		90.0	44.0		
	IQR		72.0-96.0	36.0-54.0		
	Mean rank		12.90	5.55		

P: p value for comparing between the studied groups
*: Statistically significant at $p < 0.05$

Table (6): Comparison between non-survivors in the studied groups as regards need of mechanical ventilation and length of hospital stay (N= 35)

Non-survivors			Groups		Tests of significance		Magnitude of the effect	
			Supportive N=20	Intervention N=15	Test statistic	P value	EVR	ARR (95% CI)
Need for intubation and mechanical ventilation	No	N	7	11	5.042	.025*		
		%	35.0%	73.3%				
	Yes	N	13	4			26.7 %	38.33% (7.71%-68.96%)
		%	65.0%	26.7%				
Hospital stay	Minimum		4.00	2.00	2.39	.016*	Not applicable	
	Maximum		30.00	168.00				
	Median		12.00	23.00				
	IQR		7.00-16.00	14.00-40.00				
	Mean rank		14.42	22.77				

P: p value for comparing between the studied groups
*: Statistically significant at $p < 0.05$
EVR: Experiment event rate
ARR: Absolute risk reduction
CI: confidence interval.

DISCUSSION

This study was phase II randomized clinical trial to disclose the safety and efficacy of early L-carnitine administration as an added treatment in acute AlP poisoning. At cellular levels, this study revealed the antioxidant effect of L- carnitine in the form of significant reduction in Malondialdehyde levels accompanied with significant increase in the total antioxidant capacity and reduced glutathione activity only in the L-carnitine-treated patients. Concerning outcome of the studied patients, the rate of deaths in patients on L-carnitine therapy was diminished but it did not reach a significant level. Additionally, patients received adjuvant L- carnitine regimen showed significant reduction in the need for intubation and mechanical ventilation. Whereas, they required a significantly longer duration of hospital stay. However, survivors that received L-carnitine therapy substantially showed shorter duration of hospital stay. It's worth to mention that L-carnitine administration of was safe with no reported adverse effects.

In the current study, assessment of the oxidative stress biomarkers 12 hrs after admission showed effective termination of lipid peroxidation indicated by significant reduction in the plasma MDA levels in patients received L-carnitine treatment. Alternatively,

patients who were given only the conventional supportive treatment exhibited continuous propagation of oxidative damage of free fatty acids denoted by significant increase in the MDA levels. This was accompanied with significant elevation in the total antioxidant capacity and reduced glutathione levels in patients on L-carnitine therapy. This emphasizes the involvement of glutathione in phosphine induced oxidative toxicity and the capability of L-carnitine to replenish the antioxidant defenses against PH3. Comparable findings have been shown in an animal study where, L-carnitine administration in AlP –intoxicated rats has significantly attenuated the oxidative stress and improved mitochondrial function and energy production **(Baghaei et al., 2016).** Beneficial antioxidant effects of L-carnitine have been demonstrated in toxicities caused by arsenic (**Sepand et al., 2016)** and cadmium (**Abu-El-Zahab et al., 2019).**

Though the exact mechanisms of AlP poisoning are not known, various animal and human studies had shown that AlP poisoning induces generation of superoxide radicles, cellular peroxides, hydrogen peroxide, and MDA while, it inhibits the antioxidant enzymes like glutathione, catalase and peroxidase **(Anand et al., 2012, Mehrpour et al., 2014, Anand et al., 2013).** Thereby, AlP induces oxidative stress and cellular damage via increasing lipid peroxidation, protein denaturation and hypoxic damage **(Yousef et al., 2015).**

It is clear that oxidative stress is one of the main mechanisms of AlP induced organ damage. This has encouraged many researchers to investigate the possible role of antioxidants therapy in improving the prognosis of such fatal type of poisoning **(Tehrani et al., 2013).**

L-carnitine is an essential co-factor in fatty acid metabolism which is the primary source of energy for cardiac muscles. It increases long-chain fatty acids and activated acetate transport across the inner mitochondrial membrane **(Schönfeld and Wojtczak, 2016).**

Furthermore, it has been reported that L-carnitine therapy added to aggressive supportive care has rescued two cases presented by severe myocardial cell dysfunction and shock caused by AlP ingestion. Each of them has exhibited improvement of cardiac parameters, maintenance of vital signs that ended by survival**(Elabbassi et al., 2014, Sumit and Vishnu, 2015).** Hence, this work was implemented to validate the efficacy of L-carnitine addition in severe cases of AlP poisoning presented early with shock within 3 hrs of toxic exposure.

Effects of early L-carnitine administration on outcomes of AlP poisoned patients in the present study seems promising. There was insignificant reduction in death rate in patients received L-carnitine (60%) compared with patients received only the routine supportive care (80%).

Absence of significant effects of L-carnitine on patient's survival might be attributed to the nature of our study population where only severe cases presented early with shock were recruited. Additionally, It's recognized that AlP poisoning is characterized by high mortality rate varies from 35%-

91% within the first 24 hrs **(Alnasser et al., 2018).** This high rate of deaths might be attributed to unidentified mechanisms of toxicity that could explain the observed rapid progression in the course of this poisoning which often ends with death **(Singh et al., 2015).**

To the best of our knowledge, no previous RCTs evaluated efficacy of L-carnitine in AlP poisoning. **Bhalla et al. (2017)** has stated that N-acetylcysteine (NAC) IV infusion at 150 mg/kg over 1 h, followed by 50 mg/kg over 4 hrs, and another 100 mg/kg over 16 hrs did not show any survival benefits in severe cases of AlP poisoning. Comparable results have also been reported where a randomized controlled trial of NAC infusion at a rate of 300 mg/kg for 20 hrs has showed insignificant reduction in mortality rate (30.4% compared to 43.5% in the control group) despite the observed improvement in blood pressure and oxygen saturation of the patients on NAC therapy **(Taghaddosinejad et al., 2016).**

Even with the improvement of the antioxidant status and MDA levels after N-acetylcysteine addition to supportive care of AlP poisoned patients **(Tehrani et al., 2013),** there was non-significant reduction in the rate of their deaths.

Death in AlP poisoning is mainly due to refractory cardiogenic shock, where most patients display profound drop in blood pressure which is not responsive to the usual supportive treatment (**Mohan et al., 2016).** Aluminium phosphide toxicity inhibits cytochrome c oxidase in the mitochondria of cardiomyocyte and interferes with the electron transport chain resulting in toxic myocardial necrosis similar to what occurs during ischemia **Sciuto et al., (2016).** Furthermore, **Noordali et al. (2017)** have reported that myocardial hypoxia adversely affecting electrical conduction and muscle contraction due to accumulation of long-chain acyl-CoA esters. In this regard, **Song et al. (2017)** have demonstrated that L-carnitine use in ischemic hearts has preserved mechanical function with a significant reduction of left ventricular dilatation.

Patients with AlP poisoning frequently requires endotracheal intubation and intensive care unit admission for mechanical ventilation since AlP causes hypoxia, adult respiratory distress syndrome, and disturbed conscious level **Farzaneh et al., (2018).** In this regard, the current study demonstrated significant reduction in the need for intubation and mechanical ventilation in patients received L-carnitine regimen (20% vs 56% in the control group). Certainly, this effect of L- carnitine saves the hospital resources, minimizes costs and the mechanical ventilation related complications.

Another beneficial effect of the adjuvant use of L-carnitine in the present work is significant reduction in the length of hospital stay of survivors (44 hrs vs 99 hrs in the control group). Consistent with this finding, **Oami et al., (2018)** have demonstrated depletion of carnitine in critically ill patients and they have suggested potential benefits of L-carnitine therapy in these patients. Non-survivors in the intervention group showed significantly longer hospital stay compared to patients received only the supportive

management (23 vs 12 hrs). actually, patients were stabilized with L-carnitine therapy but unexpectedly for unknown mechanism rapid deterioration and death occurs.

This study has strengths of being a randomized controlled clinical trial that was applied on a suitable sample size. Additionally, it considered the rapidly progressive course of AlP poisoning where only patients presented with shock within 3 hrs of toxic exposure were eligible. Though, it remains a single center study that necessitate further validation in other poison control centers.

CONCLUSION:

It could be deduced that early administration of L-carnitine IV infusion besides the conventional treatment in AlP poisoned patient has valuable effects. It significantly attenuated oxidative stress and lipid peroxidation. Additionally, L- carnitine therapy achieved favorable outcomes denoted by significant reduction in the need for intubation and mechanical ventilation. However, its role in minimizing mortality was not evident. Further, the use of L- carnitine was safe with no reported side effects.

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الملخص العربي

العلاج المبكر ب ل-كارنيتين في التسمم الحاد الشديد بفوسفيد الألومنيوم: تجربة سريرية عشوائية منضبطة

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المقدمة :

الألومنيوم فوسفيد هو مبيد حشرى تبخيري شائع الإستخدام للأغراض الزراعية وغير الزراعية. تستخدم حبوب الألومنيوم فوسفيد كثيرا في مصر في محاولات الإنتحار، وتشكل هذه الحبوب السبب الرئيسي لدخول العديد من حالات التسمم و كذلك الوفيات في مراكز علاج التسمم. ويعتمد علاج هذه الحالات بشكل رئيسي على الرعاية الأساسية للمريض و ذلك لعدم وجود ترياق محدد له حاليا.

الهدف من هذه الدراسة:

تقييم التأثير العلاجي و سلامة الإستخدام المبكرلدواء ل - كارنيتين كعلاج مساعد في التسمم الحاد الشديد بالالومنيوم فوسفيد على أساس دوره كمضاد للأكسدة .

مواد و طرق الدراسة:

هذه الدراسة هي تجربة سريرية عشوائية منضبطة وقد أجريت في مركز طنطا الجامعي لعلاج حالات التسمم (مستشفى الطوارئ ، جامعة طنطا) .وقد أجريت هذه الدراسة علي خمسين مريضا يعانون من التسمم الحاد الشديد بالالومنيوم فوسفيد. تم تقسيمهم بشكل عشوائي إلى مجموعتين متساويتين أ و ب بإستخدام طريقة المغلفات المختومة المبهمة والمرقمة بالتسلسل .تلقت المجموعة أ فقط العلاج الروتيني.،و تلقت المجموعة ب علاج ل-كارنيتين على النحو التالي: ٩ أمبولات (٩ جم) من -L كارنيتين في ٥٠٠ مل من محلول ملحي بنسبة ٠,٩ ٪ يعطى بالتسريب الوريدي المستمر حتى التحسن أو الوفاة و ذلك بالإضافة إلى العلاج الروتيني. و قد تم توقيع الكشف الإكلينيكي الكامل ، وعمل الفحوصات المخبرية الروتينية، و تم تقييم علامات الإجهاد التأكسدي مثل مستوي المالوندهيد في البلازما ، و مستوي إجمالي السعة المضادة للاكسدة ومستوي الجلوتاثيون لكل مريض مرة عند الدخول مباشرة وأخري بعد مرور ١٢ ساعة.

النتائج:

كشفت مقارنة علامات الإجهاد التأكسدي بين المجموعتين أ و ب بعد تلقي العلاج ب ١٢ ساعة عن إنخفاض ذو دلالة إحصائية في متوسط مستوي المالوندهيد في البلازما في المجموعة ب، مصاحبا بإرتفاع ذو دلالة إحصائية في متوسط مستوي إجمالي السعة المضادة للاكسدة و متوسط مستوي الجلوتاثيون . كما سجلت المجموعه ب إنخفاضا ذو دلالة إحصائية بشأن إحتياج المرضى إلى الأنبوبة الحنجرية و إلى جهاز التنفس الصناعي . ومع ذلك فقد أوضحت الدراسة إنخفاضا بدون دلالة إحصائية في معدل الوفيات في المجموعة ب.

الاستنتاجات :

وخلصت نتائج الدراسة إلى أن الإستخدام المبكر لدواء ل -كارنيتين عن طريق الوريد فعال و آمن كعلاج مساعد في حالات التسمم الحاد الشديد بالالومنيوم فوسفيد.