COULD N. ACETYL CYSTEINE PROLONG SURVIVAL TIME IN ACUTE ALUMINUM PHOSPHIDE POISONING AMONG EGYPTIAN PATIENTS?

By

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ABSTRACT

Introduction: Aluminum Phosphide (ALP) is one of the most common sources of pesticide toxicity. Mortality is remarkably high due to immediate release of lethal phosphine gas which causes severe oxidative stress. Unfortunately, treatment is mainly supportive and there is no specific antidote. Studies on the beneficial effects of N-acetylcysteine (NAC) in acute ALP poisoning are controversial. **Aim of the Work:** This study aimed to assess the benefits of NAC in association with adequate supportive treatment in the management of acute ALP intoxication and exploring its effect on duration of hospitalization, mortality rate and survival time among Egyptian patients admitted to "Toxicology Unit of Emergency Hospital Mansoura University". **Subjects and Methods:** This was a randomized clinical trial carried out on 60 intoxicated patients of both sexes, presented within 6 hours from ALP intoxication. All participants were divided into two groups, "NAC treated group" and "NAC non treated group". **Results:** The duration of hospitalization has diminished significantly among NAC treated group (P<0.001*). There was significant increase in the mean overall survival duration (P=0.023*) in the 1st 24 hrs. of intoxication with significant decrease in the mortality rate among NAC treated group (P=0.05*). Moreover, survival time before death was significantly prolonged among expired patients in NAC treated group (P<0.001*). **Conclusions:** The present study suggests that, early administration of high doses of NAC along with adequate supportive treatment may have a survival benefit over supportive treatment alone for the outcome in such highly fatal ALP poisoning.

Keywords: Aluminum Phosphide, Poisoning, NAC, Survival Time.

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INTRODUCTION

Aluminum Phosphide (ALP) or rice tablet is considered one of the most common pesticides that have been used to protect the stored grain from insects and rodents. It is effective and cheap. On the other hand, it does not affect seed viability as it is free from toxic residue *(Moazezi and Abedi, 2011)*. Thus, it is widely used as a pesticide as well as, it is considered a major cause of intoxication among agricultural pesticides in many countries *(Goel and Aggarwal, 2007).*

This substance next to the water, water stream or gastric acid produces a non-color, fish like smell called phosphine gas (PH3) which is immediately absorbed through the lungs and stomach causing intoxication *(Mehrpour et al., 2012)*. After ingestion, toxic manifestations develop within few minutes in the form of headache, nausea, vomiting, diarrhea, and retrosternal burning, followed by manifestations in the cardiovascular, respiratory and nervous systems. Later, disseminated intravascular coagulation, hepatic failure and renal failure may also occur *(Agrawal et al., 2015)*.

Diagnosis of intoxication with the rice tablet is mainly through history taking and physical examination. Unfortunately, treatment is mainly supportive, and no particular antidote is available. Mortality is so high, it ranges from 37% to 80%. The real number might be much higher, as fewer than 5% of cases of ALP intoxication actually reach the tertiary care center *(Bajpai, 2010)*.

Owing to its low price, easy access and high potential for intoxication, rice tablet is used in intentional acute intoxication and sometimes accidentally which finally results in death *(Mehrpour et al., 2008)*. Most of the deaths usually occur within the first few hours of ingestion because of distributive shock, heart

failure and acute breathing difficulty *(Mehrpour and Singh, 2010).*

There have been numerous pathways linked to phosphide poisoning. One of the most important mechanisms suggested is the induction of oxidative stress followed by the generation of reactive oxygen species (ROS), which cause damage to biological macromolecules leading to cellular death *(Moazezi and Abedi, 2011).*

Since ALP toxicity is linked to oxidant-free radicals with no specific antidotes thus, new therapies such as "NAC" that replenish cellular glutathione have been suggested, apart from known supporting therapies *(Agrawal et al., 2015).* It reduced myocardial oxidative injury, improved profound hypotension, and increased survival time in rats exposed to phosphide poisoning *(Bogle et al., 2006)* as well as in some human studies *(Chaudhry and Rai, 2014).* However, the results in humans are inconsistent *(Singh and Bhalla, 2015).* The NAC's role in human ALP poisoning is still not clear *(Karimani et al., 2018).*

Aim of the Work: The aim of this study was to assess the benefits of NAC in association with adequate supportive treatment in the management of acute ALP intoxication and exploring its effects on duration of hospitalization, mortality rate and survival time among Egyptian patients admitted to "Toxicology Unit of Emergency Hospital Mansoura University".

Study Design: A randomized clinical prospective comparative study was conducted from November 2018 to December 2019 on 60 poisoned patients of both sexes, who were admitted to "Toxicology Unit of Emergency Hospital Mansoura University, Egypt" suffering from acute ALP poisoning.

SUBJECTS AND METHODS

All patients were managed in emergency room (ER) and intensive care unit (ICU). Diagnosis of phosphide ingestion was confirmed by history, its typical odour, clinical presentations and some circumstantial evidence such as the presence of poison bottle or any label detected by the relatives. Patient data regarding gender, age, residence, occupation, manner of poisoning (suicidal or accidental), cause of poisoning, route of exposure, number of ingested ALP tablets, date of opening of container and period interval between exposure and starting management were collected as general demographic data. Presenting complaints, clinical manifestations and laboratory findings were recorded on admission. Therapeutic interventions, duration of hospitalization and outcome were also recorded. All data during the study had been kept confidential.

o *Interventions:*

The study subjects (60 patients) were randomly allocated using the sequentially numbered, opaque, sealed, envelopes method (Doig and Simpson, 2005) into two equal groups:

1. *NAC Treated Group:* included 30 poisoned patients who received the same conventional supportive measures plus NAC antidote {Rotacysteine 20% "Egy Pharma Company" 5gm/25ml, each ampoule = 200mg/mL} in a dose "300 mg/kg diluted in Dextrose 5% in water (D5W) along 21 hours" in the form of 3 doses *(Bhalla et al., 2017):*

1.1 *Dose 1:* 150 mg/kg IV, mixed in 200 mL of D5W and infused over 1hrs.

1.2 *Dose 2:* 50 mg/kg IV, mixed in 500 mL D5W and infused over 4 hrs.

1.3 *Dose 3:* 100 mg/kg IV, mixed in 1000 mL D5W and infused over 16 hrs.

2. *NAC Non-Treated Group:* included 30 poisoned patients who received only the conventional supportive measures.

Intravenous NAC use has been associated with the development of anaphylactoid reactions. It may occur particularly with the initial loading dose that typically responds to antihistamines and occasionally corticosteroids may be required *(Yarema et al., 2018).* All patients in the present study were carefully observed during

this period for signs of an anaphylactoid reaction. Nausea, vomiting, flushing, skin rash, pruritus and urticaria are the most common features, more serious anaphylactoid reactions are uncommon. Once an anaphylactoid reaction is under control, the infusion can normally be restarted at a lowest infusion rate. The NAC injection was diluted prior to administration, the infusion fluids used in the present study was 5% dextrose, that used once only and discarded any unused solution at the end of the session in an appropriate manner.

According to *Karimani et al., 2018,* gastric decontamination was performed for both groups in the emergency room with sodium bicarbonate (50 mEq, through the nasogastric tube) followed by coconut oil (50 ml) within the first 6 hours from ingestion. Gastric lavage using (1: 10000) potassium permanganate "KMnO$_4$" were not used in the present study because it is strong oxidizing agent that can induce hemolysis and methemoglobinemia. Moreover, an exothermic reaction while using it was noticed in some cases. In addition, it was observed that phosphine is a hard nucleophile and the free oxygen radicals released from the resolution of KMnO$_4$ do not interact with each other *(Senthilkumaran et al., 2015).* The patients were treated with the same management protocol (magnesium sulfate 1g infusion/12 hrs., calcium gluconate 1g infusion/12 hrs.) with continuous monitoring of magnesium and calcium levels, adequate hydration and supportive treatment as approved protocol for acute ALP poisoning used in "Toxicology Unit of Emergency Hospital Mansoura University" since 2018.

Sampling

Blood sampling was performed to all patients on admission before administration of any medications. Venous blood samples (5 mL) were collected in heparinized test tubes under complete aseptic conditions and plasma samples were then separated via centrifugation at 3000 rpm for 10 minutes.

Investigations

Routine investigations which include random blood glucose (RBG), complete blood picture (CBC), arterial blood gases (ABG), electrocardiogram (ECG), electrolytes, serum creatinine and liver function tests were done for each patient for initial evaluation of the poisoned patients and to reduce bias in research.

Outcome Measures

Close monitoring of pulse, blood pressure, urine output and ABG were regularly done. All patients were followed up until hospital discharge or death occurred. The primary outcome was categorized as survivor and non-survivor. The duration of hospitalization among survivors, the mean overall survival duration during the critical 1st 24 hrs. of intoxication and the mean survival time among expired patients in both groups were estimated as secondary outcomes. Significant differences between the two studied groups regarding any of these parameters is of great significance regarding the evaluation of safety and effectiveness of NAC as an adjuvant in treatment of patients with acute ALP poisoning.

Inclusion Criteria

Subjects (aged 12 years or older) with symptomatic acute ALP poisoning and a history of rice tablets ingestion presented within 6 hours from exposure with no previous medical treatment for phosphide intoxication in any medical center prior to admission were included in the study.

Exclusion Criteria

Subjects less than 12 years of age, non-manifested or with doubtful ingestion, presented more than 6 hrs of toxic ingestion or treated for ALP poisoning in any medical center prior to admission, multiple concomitant poisoning and those who refused to give consent were excluded. Pregnant and lactating women, those who are using NAC for other diseases or with history of NAC allergy, subjects with history of diabetes mellitus,

chronic heart, respiratory, kidney and liver diseases were also excluded from the study.

Study Enrollment Procedures

During the study period, each poisoned patient with the even file numbers included in NAC treated group and those with the odd file numbers regarded as NAC non-treated group. Informed written consent was taken from all participants or his/her guardian (if the patient was unable to participate in consent process). After receiving detailed information about the study, the confidentiality of the data was maintained by making code number for each patient. As well as the acceptance from the Institute Review Board (IRB), Faculty of Medicine, Mansoura University had been given code number (R/18.09.282).

Statistical analysis

The data were analyzed using the Windows Statistical Social Science Package (SPSS) software (Standard version 24). Data normality was first tested with the "Kolmogorov-Smirnov test" one-sample. Using number and percent, qualitative data were represented. Association of categorical variables was tested using "Chi-square test (χ^2)" while "Fischer exact test (FET)" and "Monte Carlo (MC) test" were used when the cell count was less than 5. Continuous variables were presented for parametric data as mean ± SD (standard deviation) and for non-parametric data as median (min-max). The two groups were compared with "Student t test" for parametric data and "Mann Whitney test (Z test)" for non-parametric data. "Kaplan-Meier test (KM)" for survival analysis and statistical significance of the discrepancies between two-group curves are calculated by "Log-Rank test". P-value was considered significant at values ≤0.05 and highly significant at values ≤ 0.001 for all the above-mentioned statistical tests done.

RESULTS

During the study period, 60 subjects of ALP poisoning presented to "Toxicology Unit of Emergency Hospital Mansoura University"

were divided into 30 patients in the NAC treated group and the other 30 were in NAC non-treated group. Regarding demographic data (Table 1), all cases were suicidal manner of poisoning. The mean age of the poisoned patients in the NAC treated group was 24.40 ± 10.55 years and in NAC non-treated group was 24.43 ± 9.66 years. Out of all poisoned patients, the majority of cases were females 38 (63.3 %), 49 cases (81.7%) were from rural areas, 30 cases (50%) were students, 51 cases (85%) were due to family troubles and 9 cases (15%) were due to financial causes. Most of the cases in both groups 50 (83.3%) had ingested from half to one tablet. All manifested studied cases were with a history of recently open the tablets container. The average time lag from ingestion to medical attention was 1.25±0.61 hrs. in NAC treated group and 1.18±5.79 hrs. in NAC non-treated one.

Regarding clinical patients' characteristics (Table 2), all patients in both groups were presented with gastrointestinal manifestations in the form of vomiting and abdominal pain. Diarrhea occurred in 23 cases (38.3%) and haematemesis occurred only in 3 (5%) of all poisoned patients. On admission, more than half of the studied cases 33 (55%) presented with no garlic odour and 36 cases (60%) with metabolic acidosis. Regarding cardiovascular complications, 33 cases (55%) presented with sinus tachycardia and 27 cases (45%) with shock that needed dopamine and noradrenaline as vasopressors. Regarding respiratory complications, 13 cases (21.7%) needed mechanical ventilation (MV) as shown in (Table 4).

Other baseline demographic data and clinical patients' characteristics shown in (Tables 1, 2) as well as laboratory investigations shown in (Table 3) were similar in both groups.

In the present study, the average ICU stay was 4.95±1.16 days in NAC treated group and about 11.29±4.63 days in NAC non-treated one with highly statistically significant

difference (P<0.001*) between both groups as shown in (Figure1) and (Table 4).

Regarding the mortality rate, 24 (80%) of poisoned patients were survived in NAC treated group and 17 (56.7%) were survived in NAC non-treated one with statistically significant difference (P<0.05*) between both groups as shown in (Figure 2) and (Table 4).

The mean duration of survival among expired patients was 16.50±4.37 hrs. in NAC treated group while the mean survival duration before death was about 3.00±1.00 hrs. in NAC non-treated one with high statistically significant difference (P<0.001*) (Figure 3) and

(Table 4). In addition, survival analysis (Table 5) showed that the mean overall survival time during strict follow up in the 1st 24 hours of intoxication was about (22.5 hrs.) in NAC treated group and about (14.9 hrs.) in NAC non-treated one, with statistically significant difference (P=0.023*) between both groups. Moreover, by doing survival function plot (Figure 4) the duration of survival during the 1st 24hrs of intoxication was increased in the expired patients of NAC treated group in comparison to NAC non-treated one along the curves of survival plot.

Table (1): Comparison between NAC treated and NAC non-treated groups regarding demographic data

Parameters	NAC treated group (n=30)	NAC non- treated group (n=30)	Test of significance	P-value
Age/ years Mean ± SD	24.40±10.55	24.43±9.66	t=0.013	0.990
Sex Male Female	11 (36.7%) 19 (63.3%)	11 (36.7%) 19 (63.3%)	χ^2 =0.00	1.00
Residence Urban Rural	6 (20%) 24 (80%)	5 (16.7%) 25(83.3%)	FET	1.00
Occupation Student Housewife Farmer Manual worker	16 (53.3%) 5 (16.7%) 6 (20.0%) 3 (10.0%)	14 (46.7%) 4 (13.3%) 9 (30.0%) 3 (10.0%)	MC	0.92
Cause of poisoning Family troubles Financial	26 (86.7%) 4 (13.3%)	25 (83.3%) 5 (16.7%)	FET	1.00
Number of tablets ingested 2 tabs 1 tab 1/2 tab ¼ tab	1 (3.3%) 12 (40.0%) 13 (43.3%) 4 (13.3%)	2 (6.7%) 11 (36.7%) 14 (46.7%) 3 (10.0%)	MC	0.946
Time lag from ingestion to medical attention (hours)	1.25 ±0.61	1.18±5.79	χ^2 =0.43	0.67

n: number, SD: standard deviation, t: student t-test, χ^2: Chi square test, FET: Fischer exact test, MC: Monte Carlo test. P is significant if ≤0.05 and highly significant if ≤0.001.

Table (2): Comparison between NAC treated and NAC non-treated groups regarding clinical patients' characteristics

	Parameters	NAC treated group (n=30)	NAC non- treated group (n=30)	Test of significance	P-value
Presenting complaints	Vomiting -Abd. Pain	16 (53.3%)	18 (60%)		
	Vomiting -Abd. Pain-Diarrhea	13 (43.3%)	10 (33.3%)	MC	0.625
	Vomiting -Abd. Pain-Haematemesis	1 (3.3 %)	2 (6.7%)		
Odour	No	16 (53.3%)	17 (56.7%)	χ^2 =0.07	0.79
	Garlic	14 (46.7%)	13 (43.3%)		
	GCS	14.70±0.95	14.93±0.25	t=1.297	0.200
	Pulse	104.57±20.51	104.27±20.51	t=0.057	0.955
	SBP	92.16±21.95	94.83±21.19	t=0.479	0.634
	DBP	56.33±16.00	57.33±15.44	t=0.246	0.806
	RR	24.66±5.50	24.50±6.00	t=0.112	0.911
	Temperature	37.50±0.00	37.50±0.00	t=0	1.0
	Metabolic acidosis	18 (60%)	18 (60%)	χ^2 =0	1.0
ECG	Sinus Tachycardia	16 (53.3%)	17 (56.7%)		
	Sinus Rhythm	14 (46.7%)	13 (43.3%)	χ^2 =0.07	0.79

n: number, Abd: abdominal, GCS: Glasgow Coma score, SBP: systolic blood pressure, DBP: diastolic blood pressure, RR: respiratory rate, ECG: electrocardiogram, t: student t-test, χ^2: Chi square test, MC: Monte Carlo test. P significant if ≤0.05 and highly significant if ≤0.001.

Table (3): Comparison between NAC treated and NAC non-treated groups regarding laboratory investigations

Parameters	NAC treated group (n=30)	NAC non treated group (n=30)	Test of significance	P-value
RBG (mg/dL)	147.50 (86-500)	147.5 (86-516)	Z=0.044	0.965
PH	7.27±0.14	7.28±0.13	t=0.325	0.746
PCO2 (mmHg)	30.46±6.94	30.43±6.76	t=0.019	0.985
HCO3 (mmol/L)	18.05±4.24	18.15±4.40	t=0.090	0.929
BE (mEq/L)	-5.50 (-18--1)	-4.50 (-17--1)	Z=0.156	0.876
PO2(mmHg)	84.86±16.81	87.56±14.44	t=0.667	0.507
SaO2 (%)	93.56±7.74	94.60±6.24	t=0.569	0.571
ALT (IU/L)	28.50 (10-1175)	28.50 (10-1165)	Z=0.156	0.876
Albumin (mg/dL)	3.72±0.49	3.77±0.44	t=0.381	0.704
Bilirubin (mg/dL)	0.40 (0.10-6.10)	0.50 (0.10-6.20)	Z=0.246	0.806
INR (ratio)	1.22±0.30	1.20±0.27	t=0.279	0.781
Creatinine (mg/dL)	0.70 (0.20-3.40)	0.70 (0.20-3.38)	Z=0.512	0.609
WBC (cells/mm3)	9.00 (5-23)	9 (5-23)	Z=0.096	0.923
Hemoglobin (gm %)	10.78±1.66	10.76±1.59	t=0.048	0.962
RBC (million/mcL)	4.00±0.48	4.06±0.47	t=0.537	0.593
Platelet (x 10^9 per liter)	210.50±74.09	215.40±77.24	t=0.251	0.803
Na (mmol/L)	140.71±4.57	140.27±4.49	t=0.370	0.713
K (mmol/L)	3.61±0.43	3.61±0.470	t=0.029	0.977
Ca (mmol/L)	8.15±0.90	8.15±0.94	t=0.000	1.00
Mg (mmol/L)	1.54±0.45	1.56±0.45	t=0.171	0.865

n: number, RBG: random blood glucose, BE: base excess, SaO2: oxygen saturation, ALT: Alanine transaminase, INR: international normalized ratio, WBC: white blood cell, RBC: red blood cell, t: student t-test, Z: Mann Whitney test. P is significant if ≤0.05 and highly significant if ≤0.001.

Table (4): Comparison between NAC treated and NAC non-treated groups regarding treatment procedures and outcome measures

Parameters	NAC treated group (n=30)	NAC non- treated group (n=30)	Test of significance	P-value
Vasopressors				
No	16 (53.3%)	17 (56.7%)	$\chi^2 =0.07$	0.795
Dopamine +Noradrenaline	14 (46.7%)	13 (43.3%)		
Mechanical ventilation				
Yes	7 (23.3%)	6 (20.0%)	$\chi^2 =0.098$	0.754
No	23 (76.7%)	24 (80.0%)		
Average ICU stay (days)	4.95±1.16	11.29±4.63	t=6.45	<0.001*
Mortality rate				
Survived	24 (80%)	17 (56.7%)	$\chi^2 =3.77$	0.05*
Died	6 (20%)	13 (43.3%)		
Survival time before death (hours)	16.50±4.37	3.00±1.00	t=10.88	<0.001*

n: number, SD: standard deviation, ICU: intensive care unit, t: student t-test, χ^2: Chi square test. P is significant if ≤0.05 and highly significant if ≤0.001.

Table (5): Survival analysis among NAC treated and NAC non- treated groups during the 1ˢᵗ 24hs of intoxication

Overall survival / 1ˢᵗ 24 hours of intoxication					
Groups	Mean Survival time	Std. Error	95% CI	Log rank test	P - value
NAC treated	22.5	0.69	21.13-23.87	5.16	0.023*
NAC non-treated	14.9	1.9	11.17-18.63		

Std. Error: standard errors, CI: confidence intervals. P is significant if ≤0.05 and highly significant if ≤0.001.
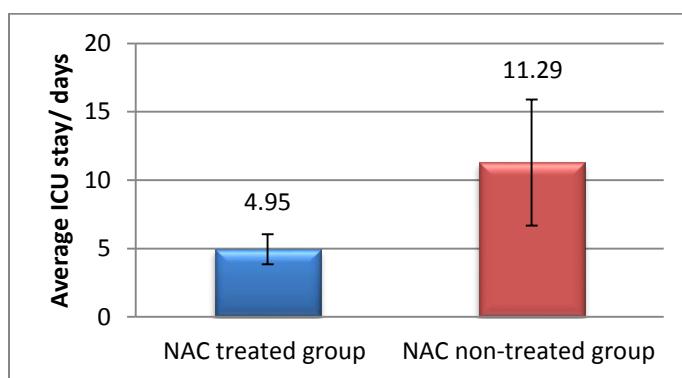

Figure (1): Average ICU stay in hospital among NAC treated and NAC non-treated groups
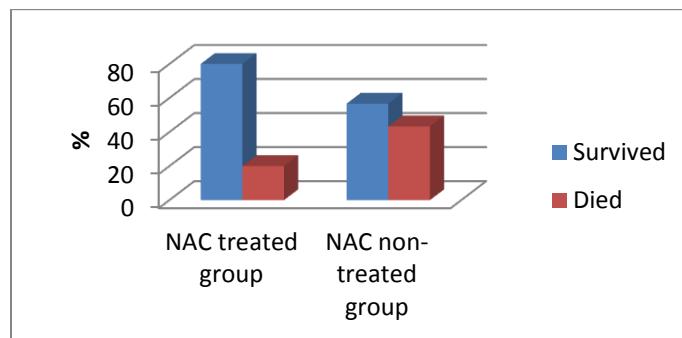

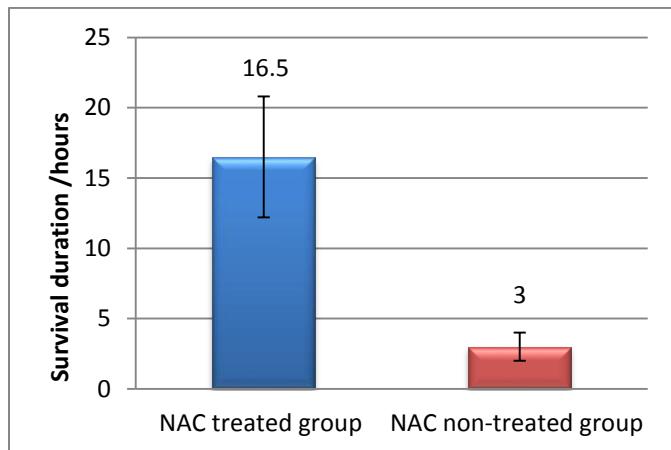**Figure (2): Survivors versus expired among NAC treated and NAC non-treated groups**

Figure (3): Survival duration before death among expired patients in NAC treated group versus NAC non-treated group
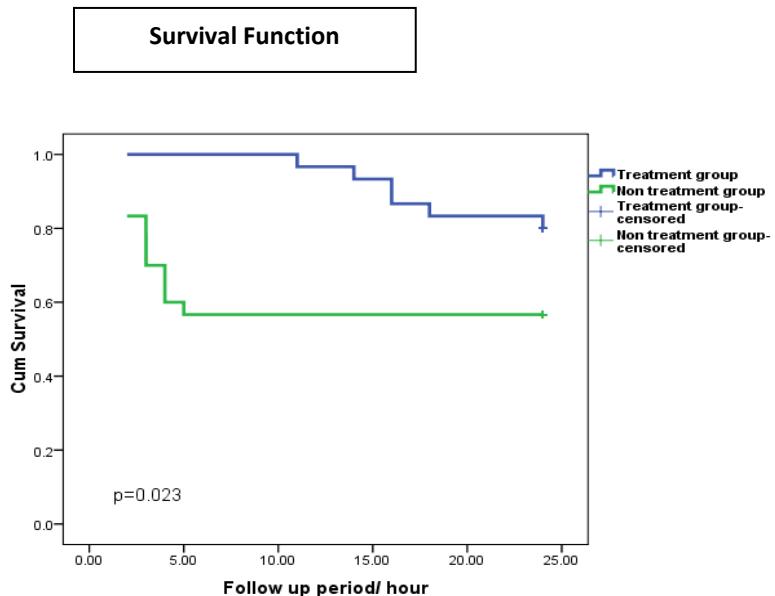

Figure (4) Survival function plot shows the overall survival time is prolonged in the NAC treated group than the NAC non-treated group with increased survival duration in the expired patients of NAC treated group during the 1st 24 hrs of intoxication.

DISCUSSION

The increase in ALP intoxication and its high mortality are considered a major concern in developing countries for health professionals. Since there is no definite antidote for the management of acute ALP poisoning, it is necessary to look for other modalities of treatment to reduce morbidity and mortality rate *(Bajpai, 2010)*.

The mechanism of ALP toxicity includes inhibition of oxidative phosphorylation and cytochrome-c oxidase enzyme that produce cellular respiration failure and induce oxidative stress causing lipid peroxidation, cell membrane protein denaturation and hypoxic damage to the cells *(Hsu et al., 2000)*. From this point of view, antioxidant therapy might have a therapeutic benefit in acute ALP intoxication. Many studies assessed antioxidants usage in the management of acute ALP poisoning. These studies reported that melatonin, glutathione, and magnesium had

protective role in the oxidative damage caused by phosphine (*Hsu et al., 2002*).

The present work was carried out to evaluate the role of NAC as a powerful antioxidant in association with adequate supportive treatment in the management of acute ALP intoxication and exploring its effects on duration of hospitalization, mortality rate and survival time among Egyptian patients admitted to "Toxicology Unit of Emergency Hospital Mansoura University.

On analysis, demographic data, clinical features, and baseline laboratory investigations between both NAC treated and NAC non-treated groups were similar, that is to reduce bias in research. Regarding demographic data, the present study showed that, the majority of patients were young (mean age was 24 years), from rural areas as rice tablet is considered one of the most frequently used pesticides. Predominantly female students due to family troubles, this may be due to its low price and easy accessibility as well as the psychological liability of the females. In contrast, it was found in the study of *Mathai and Bhanu, 2010* that most of the patients were young males because of their work in the fields of agriculture and grains storage houses where it is commonly used.

All the cases manner of poisoning was suicidal with average time lag between ingestion and medical attention about 1h. *Gunnell et al., 2007* reported that most of the cases were suicidal manner of poisoning and few cases were inadvertently exposed to ALP.

In the present study, the poisoned cases had ingested from about ¼ to 2 recently opened rice tablets with no garlic odour appears in 55% of poisoned cases. *Bogle et al., 2006* had observed that, there was no distinctive garlic odour of phosphine in their studied cases also. However, "off gassing" of phosphine expired in patient's breath particularly in the absence of respiratory safety, may be a potential threat. Regarding other clinical manifestations, vomiting and abdominal pain, impaired sensorium, hypotension, tachycardia, tachypnea, and hypoxemia are the most common manifestations.

Most of the studied cases (60%) presented with metabolic acidosis (PH 6.9-7.34) mostly due to lactic acid accumulation caused by histotoxic hypoxia and poor tissue perfusion. This agrees with *Jaiswal et al., 2009* who reported that all ALP intoxicated patients presented with severe metabolic acidosis. Moreover, about 33 cases (55%) presented with sinus tachycardia. According to *Gurjar et al., 2011*, temporal correlation in ECG changes in ALP poisoning showed that during the initial 3–6 h, sinus tachycardia is predominant.

Regarding routine laboratory investigations done on admission, there were not statistically significance differences between both groups. Regarding treatment procedures, about 45% of patients needed vasopressors and about 21.7% needed MV also *Mathai and Bhanu, 2010* had observed that 89% of ALP poisoned patients were severely hypotensive due to distributive shock and *Louriz et al., 2009* concluded that, MV was required for 80% of patients.

According to *Bajpai, 2010*, the mortality rates published in the literatures for ALP poisoning vary from 37% to 80%. The mortality rate in the present study was 31.7%. Moreover, 80% of ALP poisoned patient survived in NAC treated group and 56.7% survived in NAC non-treated one with statistically significant difference (P<0.05) between both groups.

Antioxidants play a significant role in preventing free radicals' formation and scavenging other toxic oxidizing agents. They act as reducing agents that would increase the tolerance of phosphide poisoned cases (*Atkuri et al., 2007*). N-acetylcysteine is one of the most promising antioxidants that has been tried in experimental and human studies, it stimulates endogenous glutathione synthesis. Both glutathione and its counterpart NAC counteract ROC's harmful effects by either

restoring oxidative damage or directly scavenging radicals of *oxygen (Yedjou et al., 2008)*.

The present study showed that NAC treated group along with supportive treatment had improved ALP poisoned patients' primary outcome over supportive treatment given alone in control NAC non-treated group and no adverse effects for NAC administration were recorded. The duration of hospitalization decreased among survivors (4.95±1.16 days) in NAC treatment group compared to NAC non-treated one (11.29±4.63 days) with high statistically significant difference (P<0.001*). Also, by comparing the survival functions between the two groups during the critical period of poisoning which is the first 24hs, as most of the deaths occurs (1-24 hrs.) from toxicity *(Trakulsrichai et al., 2017)*, there was increase in the mean overall survival time among NAC treated group (22.5 hrs.) versus NAC non-treated one (14.9 hrs.) with statistically significant difference (P=0.023*). In addition, the mean survival duration was prolonged (16.50±4.37 hrs.) among expired patients in NAC treated group compared to NAC non-treated one (3.00±1.00 hrs.) with high statistically significant difference (P<0.001*).

Similarly, *Azad et al., 2001, as well as, Agarwal et al., 2014* had mentioned that, treatment with NAC in ALP intoxication significantly increased the duration of survival and lead to early stabilization of heart rate, blood pressure and ECG by decreasing myocardial oxidative injury in rats. Moreover, *Tehrani et al., 2013, Taghaddosinejad et al., 2016, Oghabian and Mehrpour, 2016* as well *as Nakhaee et al., 2017* had concluded that, NAC treatment was associated with hemodynamic stabilization during the 1st 24 hours after intoxication and decrease in both mechanical ventilation rate and duration of hospitalization.

However, studies on the beneficial effects of NAC are controversial and show conflicting results *(Chaudhry and Rai, 2014)*. A study carried out by *Bhalla et al., 2017* on 50 severely ALP intoxicated cases, the rate of mortality was 87.5% in treatment group and 88.5% in placebo group. They concluded that, NAC did not improve severe ALP poisoning outcome. In another study done by *Ahmadi et al., 2018*, NAC was examined for reducing ALP causing cardiogenic shock and cardiotoxicity in rats revealing no significant effects.

The limitations of this study were small sample size in both studied groups. Since some of the severally ill patients in NAC treated group died before completing the full dose regimen of NAC, and as noticed, NAC prolonged survival duration among expired cases and prolonged the overall survival time in the 1st 24 hrs. of intoxication among NAC treated group, this indicates that, dosing regimen used in the present study may not be ideal for severe ALP intoxicated patients.

CONCLUSIONS

Although the well established role of oxidative stress pathway in Aluminium Phosphide toxicity confers biological plausibility to the use of antioxidants, there are insufficient human studies showing a significant mortality benefit. The present study suggests that, early administration of high doses of N-acetylcysteine along with adequate supportive treatment may have a survival benefit over supportive treatment alone for the outcome in such highly fatal poisoning.

RECOMMENDATIONS

According to the present study, the following guidelines are recommended: (1) Early intervention giving the full 3 doses of IV "NAC" beginning with the first dose within the first 3–6 hrs. of intoxication as an adjuvant to the standard supportive measures. (2) larger doses of NAC (140 mg / Kg IV infusion as a loading dose followed by 70 mg / Kg IV infusion every 4 hours up to 17 doses according to *Tehrani et al., 2013*) in further studies may be promising to optimize management

protocols for ALP poisoning. (3) Several clinical trials on larger scale with bigger sample sizes and further mechanistic hypothesis are required to investigate why ALP poisoned patients may die after initial stabilization for a considerable time after adding NAC to aggressive supportive care.

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