

Study of the Role of N-Acetyl Cysteine in Phosphide Poisoning

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Abstract

Compounds containing phosphide used as rodenticide are among most fatal poisonings encountered in Poisoning Control Center, Ain Shams University Hospitals (PCCA) Cairo, Egypt. Its toxicity is associated with challenging oxidative damaging effects that involve all tissue cells. Patients develop severe hypotension and metabolic acidosis. No available data about specific antidotes for these compounds, however we assume that antioxidants may play a beneficial role in improving intoxicated patient outcome. N-acetyl cysteine (NAC) is supposed to have a protective role.

Objective: To evaluate the role of antioxidant N-acetyl cysteine (NAC) in improving outcome of phosphide intoxicated patients.

Methods: The study is double blind randomized clinical trial, carried on patients presented to PCCA over 3 years period (2015-2017) with severe zinc and aluminum phosphide intoxication. They are randomly classified to NAC treated group (receiving conventional treatment plus NAC intravenous (IV) infusion in a dose of 300 mg/kg over 20 hours then 150 mg/kg/day until improvement) and placebo group (receiving conventional treatment plus saline IV infusion). Clinical data such as (age, sex, mode of poisoning and vital data), blood PH, liver function test, ECG, usage of mechanical ventilation, mortality and period of stay were recorded and compared for each group.

Results: statistical analysis revealed significant decrease in mortality and mechanical ventilation in patients with the group of NAC administer. However no significant difference was observed regarding period of stay.

Conclusion: The study concluded that NAC may have good role in decreasing mortality and incidence of mechanical ventilation in phosphide poisoning patients.

Keywords: Phosphide; Aluminum; Mortality; Acidosis; Shock; NAC; Ventilation

Introduction

Rodenticide is a common fatal ingested poison and its use as agents of deliberate self-harm is on the rise. The number of cases of rodenticide poisoning is globally rising, with around 300,000 cases being reported every year [1]. Rodenticides are composed of super warfarins, thallium, barium carbonate, aluminum phosphide and zinc phosphide. They are used in some developing countries as they are inexpensive, effective indoor and outdoor agents [2]. Due to its high fatality the need for an antidote is urgent and imperative [3].

Phosphide in contact with water or acid liberates the highly toxic phosphine gas. Phosphine inhibits cellular oxygen utilization by its effect on mitochondria, and also by decreasing the activity of cytochrome oxidase [4]. It also produces oxidative stress and liberates highly reactive hydroxyl radicals. Reactive oxygen species toxicity is believed to be the cause in the genesis of phosphide induced toxicity. Lipid peroxidation and other oxidant mechanisms subsequently lead to cellular injury [5].

The main cause of death is a refractory cardiogenic shock. Moreover, other contributing factors include severe hypotension, refractory metabolic acidosis, hepatic necrosis, renal failure and

adrenal gland damage. Since the cardiovascular system is the main target of this poison, various electrocardiographic changes including dysrhythmias may occur by this fatal poisoning [6].

At present, no definite antidote for phosphide poisoning has been identified. Antioxidant agents seem to usefully reduce the toxicity. Glutathione as a main antioxidant defense is reduced by phosphide poisoning. NAC is an important antioxidant and a cytoprotective agent that replenishes intracellular glutathione and counteracts damaging effects of reactive oxygen species by either repairing the oxidative damage or directly scavenging oxygen radicals [7]. In view of the high mortality associated with phosphide consumption, and the relatively benign adverse effect of NAC, physicians began to treat patients admitted with phosphide poisoning with NAC [8].

The aim of this work is to evaluate the role of N-acetyl cysteine in management of phosphide poisoning in patients with zinc and aluminum phosphide acute intoxication *via* a randomized controlled clinical trial.

Methods

This study was a double blinded randomized clinical trial conducted on patients suffering from acute severe phosphide poisoning who were admitted within 12 hour after exposure to the Poison Control Center of Ain Shams University Emergency Hospital, Cairo, Egypt, between

January 2015 and December 2017. The diagnosis in all cases was established on the basis of reliable history of intake of phosphide substance and clinical symptoms and signs. The severity was determined by using poisoning severity score with severe cases only included in the study. Patients with history of diabetes mellitus, cardiovascular, respiratory, renal, hepatic diseases and unreliable history were excluded from the study.

A total of 60 patients were included in the study. The study patients were randomly allocated into two groups (using excel randomization sheet with allocation concealment): (NAC treated group) included 26 patients received conventional treatment plus NACIV infusion and (placebo group) included 34 patients received (conventional treatment and saline IV infusion). The two groups were not equal in size because we stopped the study before the end due to unavailability of NAC due to import issues.

All patients received the conventional treatment, which included all or some of the following as indicated: gastric lavage with sodium bicarbonate 5% if delay less than 2 hours, hydrocortisone (200 mg initially followed by 100 mg every 6 hours), noradrenalin infusion to treat shock, NaHCO₃ administration for treatment of acidosis, and magnesium sulphate (1 g initially followed by 1 g every 6 hours).

In addition to the conventional treatment, NAC treated group received NAC IV infusion (Rotacysteine 25 ml ampoule: each ampoule contain 5 gm NAC produced by Arabcomed-Egypt Rotabiogen for pharmaceutical invest) in a dose of 300 mg/kg for 20 hours then 150 mg/kg/day until recovery. The placebo group received saline solution IV infusion and it was matched to the study drug for color, consistency and amount.

All patients were subjected to full history taking (including age, gender, circumstances of poisoning and history of medical diseases); complete physical examination (including regular monitoring of vital signs, general clinical examination and presence or absence of mechanical ventilation). Arterial blood samples were obtained from each patient for blood gas analysis, whereas venous samples were used for estimation of liver enzyme. Electrocardiogram (ECG) done for all patients at admission and repeated if there was evidence of arrhythmia on the cardiac monitor. All the patients were prospectively monitored by qualified physicians with regular measurement of their vital data and oxygen saturation *via* a bedside monitor, and they were followed up until discharge from the hospital.

The primary outcome was mortality, whereas secondary outcome measures included the length of hospital stay and need for mechanical ventilation.

Parameter	Placebo Group no=34	NAC Treated Group no=26	Total no=60	t	p
Shock	29 (85.3%)	17 (65.4%)	46 (77%)	3.3	0.07
Metabolic acidosis	26 (76.5%)	21 (80.8%)	47 (78%)	0.2	0.7
ECG	9 (26.5%)	4 (15.4%)	13 (22%)	1.1	0.3
Liver affection	8 (23.5%)	13 (50%)	21 (35%)	4.5	*0.03
Mechanical ventilation	25 (73.5%)	10 (38.5%)	35 (58%)	7.5	*0.006

Table 2: Statistical analysis of Clinical, laboratory parameter, ECG and intervention of the two studied groups, *p ≤ 0.05=significant.

Statistical analysis: All data were collected either as continuous variables or as categorical variables. All data were analyzed with SPSS software version 12. The data were expressed as mean and SD for continuous variables and as frequency and percentage for categorical variables. Chi-square test was used for statistical comparison of qualitative variables and t-student test was used for statistical comparison of continuous variables. A P value less than 0.05 were considered as significant.

An informed consent was obtained from alert patients or their first-degree families or relatives. All data were kept confidential during the study. The study protocol was approved by the ethical committee of poisoning control center.

Results

60 Patients with severe phosphide poisoning were admitted during the study period. The mean ages in both groups were 26 ± 15 years. Most of the patients were male (58%), the majority of patients were suicidal (88%) and only (12%) presented with accidental poisoning (Table 1).

Mean Age ± SD	26 ± 15	
Sex		
Male	35	(58%)
Female	25	(42%)
Mode of Poisoning		
Suicidal	53	(88%)
Accidental	7	(12%)

Table 1: Age, sex and mode of poisoning of 60 phosphide poisoning patients, *p ≤ 0.05=significant.

This study revealed that 77% of the patients presented with shock, 78% presented by metabolic acidosis, 22% had ECG abnormalities and there was no significant difference between both groups as regards shock, metabolic acidosis and ECG abnormalities. Thirty five percent (35%) of the patients presented with liver affection with significant increase in NAC treated group. Fifty eight percent (58%) of the patients received mechanical ventilation and there significant decrease in mechanical ventilation in NAC treated group (Table 2).

The study revealed that the mortality rate was 55% and there was significant decrease of the mortality in NAC treated group (34.6%) when compared with placebo group (70.6%). Our study revealed that

the mean period of stay in placebo group was 2 ± 1.6 days, while in NAC treated group was 3.5 ± 2.1 days and there was significant increase in period of stay in NAC treated group (Table 3).

	Placebo group no=34	NAC treated group no=26	Total no=60	t	p
Death	24 (70.6%)	9 (34.6%)	33 (55%)	7.7	*0.005
Period of stay	2+1.6	3.5+2.1	-	3.1	*0.003

Table 3: Statistical analysis of outcome and period of stay of the two studied groups, *p ≤ 0.05=significant.

By analysis the survived patients we found no significant difference between survived patients who received NAC and those who don't

receive NAC as regards period of stay and mechanical ventilation (Table 4).

	Survived with NAC no=17	Survived with no NAC no=10	Total no=27	t	p
Mechanical ventilation	1 (6%)	2 (20%)	3	1.3	0.3
Period of stay	4.7 ± 2.6	4 ± 2.9	-	0.7	0.5

Table 4: Statistical analysis of mechanical ventilation and period of stay of the survived patients, *p ≤ 0.05=significant.

Discussion

Phosphide either aluminum or zinc phosphide is cheap, effective or does not affect seed viability. Its use has become widespread and is now a common mode of suicide in the agricultural community, usually involving young adult population from rural areas [9]. Due to increase in the percentage of phosphide poisoning, its high mortality and no specific antidote available, the evaluation of other treatment modalities is necessary in order to decrease the rate of mortality and/or morbidity [10].

This study revealed that the mean ages in both groups were 26 ± 15 years, most of the patients were male (58%), and the majority of patients were suicide (88%). These findings agree with previous study of 97 Patients poisoned with phosphide and found 57.7% of the patients were Males, 94.8% were suicidal and 82.5% of the suicide patients were young ages (18-40 years) [11]. While other study found that the ages in the case and control groups in phosphide poisoning patients were ranged from (18–37 years) and most of the patients were female (56.5%)[5].

This study found that shock and metabolic acidosis were the most common abnormalities and no significant difference between both groups as regards presentation with shock, metabolic acidosis, ECG abnormalities and this is ensured that both groups had the same severity of intoxication. Similar study found that the most common clinical manifestations on admission were gastrointestinal disturbances including vomiting (93%) and abdominal pain (32%), but during the hospitalization, hypotension (100%) and metabolic acidosis (73%) were the most common manifestations [7]. While in contrast previous study of 100 patients with phosphide poisoning found that emesis was a common presenting symptom (67%) and the liver was the main organ involved. Only one of the hundred patients presented with altered sensorium [8]. Also other study found that in phosphide poisoning patients; initially they developed acute liver failure and later progressed to multisystem organ failure [11].

This study revealed that the mortality rate was 55% with significant decrease in mortality and mechanical ventilation in NAC treated group. Similar results obtained by previous study of 97 patients

poisoned with phosphide rodenticide and noticed 35.7% mortality and patients who presented early and started on N-Acetyl cysteine had good prognosis [11]. Also another study of 100 patients with phosphide poisoning found that patients who had received NAC had lower peak values of Aspartate Transaminase/Alanine Aminotransferase (AST/ALT), shorter hospital stay, lower mortality (89% of the deaths were in patients who had not been treated with NAC) and concluded that NAC may have a role in the management of phosphide poisoning [8]. Moreover other animal study found that, NAC had a protective role against cardiovascular complications of phosphide intoxication by protecting heart cells from the oxidative stress induced by phosphine [12]. Also a study of 37 patients with phosphide poisoning showed significantly lower rates of intubation, ventilation, shorter duration of hospitalization and lower mortality in phosphide-poisoned patients treated with NAC. Also the same study found smaller increase in total antioxidant capacity in NAC treatment group compared to the control group and concluded that NAC may have a therapeutic effect in acute phosphide poisoning [7]. In contrast lesser mortality rate (18%) was observed in a study of 100 patients with phosphide poisoning [8], and another study of 46 patients with phosphide poisoning found lesser mortality rate (27%) with no significant difference as regarded the mortality between the patients who received NAC and those who received conventional treatment only [5].

This study showed that the mean period of stay in NAC treated group was 3.5 ± 2.1 days, while in placebo group was 2 ± 1.6 days and there was significant increase in period of stay in NAC treated group. This is explained by the higher mortality rate in placebo group and most of them died in the second day of admission which explain the shorter period of stay, this is proved also by No significant difference between survived patients who received NAC and those who did not receive NAC as regards period of stay.

Conclusion

In conclusion, oxidative stress is the cause of the mortality associated with phosphide poisoning, NAC administration as an antioxidant should be considered in the management of this poisoning

and the study concluded that NAC had good role in decreasing mortality and incidence of mechanical ventilation in phosphide poisoning patients.

Limitations of the Study

The number of patients in both groups was not equal because we couldn't complete the study to the end due to problem in the supply of NAC ampoule in Egypt due to import and financial issues.

Acknowledgment

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Conflicts of Interest

Authors declare that we have no conflict of interest.

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