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ORIGINAL ARTICLE

The Effect of Hyperinsulinemia-Euglycemia on Acute Aluminum Phosphide Poisoning: A Clinical Trial

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Abstract

Background: Aluminum Phosphide toxicity, a common deliberate hazard, often leads to death due to the absence of a specific antidote for treatment. This study aimed to assess the efficacy of the Hyper Insulin Euglycemia protocol combined with vitamin E and N-acetyl cysteine in the treatment of patients with acute Aluminum Phosphide poisoning.
Methods: In this incidental prospective clinical trial, 76 individuals with toxicity were enrolled and assigned to two groups: one treatment group receiving glucose, insulin, and potassium administration along with vitamin E and N-Acetyl Cysteine, and one control group primarily managed with supportive treatments. Signs and symptoms at arrival and during hospitalization, complications, and outcomes were recorded and compared between these two groups to identify any potential effects of vitamin E and the protocol for toxicity treatment.
Results: This study investigated the mortality and safety of therapy in 76 poisoning patients with an average age of 28. The mortality rate in the treatment group was 26% lower than in the control group (p-value: 0.058). Furthermore, this research observed a significant increase in systolic blood pressure during hospitalization in the treatment group. Regarding pH and bicarbonate levels, the treatment group exhibited less metabolic acidosis. In contrast to the case group, the therapy group's bicarbonate levels significantly increased throughout hospitalization.
Conclusion: The use of vitamin E and the protocol, along with symptomatic and supportive treatments, in acute Aluminum Phosphide toxicity among the treatment group in this study resulted in a significant increase in systolic blood pressure, longer hospitalization duration, and lower death rates.

Keywords: aluminum phosphide toxicity, glucose-insulin- potassium, hyper insulin euglycemia, rice tablet

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INTRODUCTION

Pesticides are commonly available in rural Asian areas, considered the leading cause of poisoning after deliberate ingestion [1]. One of the most effective pesticides is aluminum phosphide (ALP), known as rice tablet in Iran; due to its use as a grain and rice protector, people keep this tablet in their storage facilities [2]. Urea, alp, and ammonium carbonate are the contents of these greenish-gray, garlic, or rotten fish odor rice tablets [3].

In contact with gastric acid and moisture, the ALP starts a chemical reaction during which highly toxic phosphine gas (PH3) is produced [3]. The primary mechanism of action of PH3 is inhibiting cytochrome-c oxidase enzymes in mitochondria, leading to cellular hypoxia and cell death. Correspondingly, increased free radicals formation, induction of oxidative stress by catalase inhibition, cholinesterase enzyme inhibition, hemolysis, and methehemoglobinemia are other reported mechanisms of ALP systemic toxicity [4].

ALP toxicity happens by ingestion, phosphine gas inhalation, and rarely skin absorption, affecting almost all body organs. Circulatory shock, gastrointestinal upset, respiratory failure, and dysrhythmias are the most common signs patients present in the hospital. As no specific antidote exists for ALP toxicity, the treatment mainly remains supportive such as mechanical ventilation and vasopressor drugs. Some reported recommended therapeutic methods available targeting to remove toxins from the gastrointestinal tract or circulatory system and to scavenge free radicals, which include magnesium sulfate intravenous injection, sodium bicarbonate or coconut oil, gastrointestinal decontamination with potassium permanganate, gastric ventilation, intravenous lipid

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emulsion, N-acetyl cysteine, whole blood exchange transfusion, and extracorporeal membrane oxygenation. Nevertheless, these methods stay controversial or need further studies for proof [1].

Among all the complications patients face during ALP toxicity, cardio-circulatory collapse and metabolic acidosis are the most crucial ones, hardly responsive to conventional therapies [5]. Based on reported studies on animals and humans, exogenous insulin administration by use of glucose, insulin, and potassium(GIK), causes hyperinsulinemia-euglycemia (HIE) condition that has shown beneficial positive inotropic effects in patients with severe beta-blocker and calcium channel blocker toxicities [1]. GIK administration as a possible treatment of ALP toxicity was first used in 2008 in a small group of patients [5]; other studies claimed favorable outcomes and extended hospital stay for these patients [5]. This study conducted a randomized clinical trial prospective intervention among patients with acute AlP poisoning admitted to the Intensive Care Unit (ICU) of Lohman Hakim Hospital Poison Center, Tehran, Iran, during 2013-2014 to evaluate the efficacy of the HIE protocol in combination with vitamin E and N-Acetyl Cysteine(NAC) –as antioxidant agents–in patients with acute AlP poisoning.

METHODS

Study design

This incidental clinical trial used a prospective open-label strategy using a sample of patients with ALP ingestion. The study was conducted at the toxicology department of Loghman-Hakim Hospital, Tehran, Iran. This toxicology department is Tehran's leading referral center for poisoned patients, receiving around 24,000 to 27,000 intoxicated people each year, over 10,000 to 12,000 of whom are hospitalized [6]. The Ethics Committee of the Shahid Beheshti University of the Medical Sciences approved the study's protocol.

Study participants

Patients with AlP poisoning were included in this trial from March 2013 to February 2014. The patients' or their companions' history, clinical findings (signs and symptoms), such as smelling garlic from the patient's mouth, hypotension, metabolic acidosis, and a positive silver nitrate test (SNT), were used to make the diagnosis of AlP poisoning. Fluids, inotropes, mechanical ventilation, electrolyte balance maintenance, and anti-arrhythmic medications were administered to all patients as needed. Gastric lavage was used to decontaminate the gastrointestinal tract within 1 to 2 hours following consumption. Participants who met the following criteria were excluded from the study: 1. Diabetes, renal failure, and hepatic, respiratory, or cardiac disease in the past, 2. Malignancy history, 3. Incomplete treatment, due primarily to death within the first two hours 4. Any additional toxicity coexisted 5. The vegetable origin of the rice pills ingested.

Blinding to randomization was not practicable due to the considerable differences in the therapies and investigators-participants' involvement. The patients were assigned to the intervention or control groups based on the time they were admitted to the hospital. If patients were included in the treatment group, informed written consent forms were obtained from participants or the next of kin.

Clinical and laboratory measurements

Upon arrival, a questionnaire was filled out by the patient or companions to acquire demographic information about the patients, such as age and sex, as well as information about the number of pills taken, the interval between taking the pills and being referred to the hospital, and whether or not vomiting occurred after taking the pills. On arrival, vital signs were also noted. Routine blood sample testing, such as blood sugar, urea, creatinine, liver tests, blood electrolytes of sodium, potassium, calcium, phosphorus, and magnesium, coagulation test, and measurement of hemoglobin, hematocrit, platelet count, white blood cell count, as well as arterial blood gases, were performed on patients upon admission.

Interventions

The severity of clinical manifestations and the need for intubation and mechanical ventilation determined the admission criteria for ICU patients. Upon the final diagnosis of rice pill poisoning and transfer to the ICU, the patients were randomly divided into control and treatment groups. Common treatments administered to both the control and treatment groups included the following:

- Activated charcoal (1g/Kg, 50-100 grams)
- Gastric lavage with potassium permanganate solution (1:10000)
- Administration of normal saline (10-20mL/Kg, IV)
- Intravenous (IV) sodium bicarbonate (1mEq/Kg)
- Calcium gluconate
- Vaporizer
- NAC infusion (140 mg/kg initially, followed by 17 doses of 70 mg/kg)
- Vitamin E Intramuscular (IM) 400 IU/BD

In the treatment group, an IV crystal insulin delivery protocol was employed with an initial dosage of 1 unit/kg, and dextrose at a dose of 1g/Kg if the blood sugar level was less than or equal to 100 mg/dL. Additionally, a maintenance dose of insulin (0.5-1 IU/Kg) was administered via IV infusion, and the timing of these doses was determined based on electrolyte and blood sugar test results. It's important to note that serum potassium levels were monitored hourly, and intravenous potassium chloride was administered when hypokalemia was detected.

Outcomes

The study's primary outcome was a comparison of mortality rates between the case and control groups. Secondary outcomes were changes in systolic and diastolic blood pressure, arterial blood gas measurements, the necessity for mechanical ventilation, the duration of intubation, and the length of hospital stay.

Statistical analysis

The Kolmogorov-Smirnov test was employed to ensure that the data were normally distributed. Statistical tests such as the Student t-test, One-way ANOVA, Fischer Exact test, Chi-Square, and Mann-Whitney tests were performed depending on the data distribution. Statistical significance was assigned to all differences with $P \leq 0.05$. For statistical

analysis, SPSS software Version 22 was used.

RESULTS

Following the exclusion of ineligible participants, a total of 76 individuals with AlP toxicity were included in this study, comprising 44 males (57.9%) and 32 females (42.1%). All patients had ingested AlP with the intent of self-harm. The mean age of the participants was 28 ± 11, with no significant age differences observed between genders. Participants were randomly assigned to either the control group, consisting of 15 individuals (comprising nine males and six females) with an average age of 32 ± 14 years, or the treatment group, which included 61 individuals (comprising 35 males and 26 females) with an average age of 27 ± 10 years. Notably, there were no significant age or gender disparities between the treatment and control groups. Among the participants, the most common method of poisoning involved the ingestion of two rice tablets (22.3%), with only 4 individuals (5.3%) dissolving the tablets in water, all of whom were part of the treatment group. The remaining participants swallowed the tablets whole, without dissolving them. The mean duration of hospitalization did not exhibit a significant difference between the treatment and control groups. Vomiting was the predominant symptom following admission, and the average heart rate at arrival was consistent in both groups. Laboratory testing results, encompassing glucose, urea, creatinine, liver enzymes, serum electrolytes, calcium, and magnesium, did not reveal significant differences between the groups. Subsequently, the mean blood pressure of hospitalized patients was assessed in both the control and treatment groups at arrival and at 24, 48, and 72 hours. No significant differences were observed between the case and control groups in terms of mean blood pressure. However, post-hospitalization, the systolic blood pressure in the treatment group exhibited a notable increase from 91 ± 16 to 114 ± 21.

Furthermore, the study compared the initial and final arterial blood gas (ABG) test results. Table 3 and Figure 1 provided an overview of the mean ABG parameters for the case and control groups. At the conclusion of the treatment,

Table 2. Comparison of systolic and diastolic blood pressure in patients with acute poisoning by AlP in the Case and control groups on consecutive days.

		Case	Control	P-value*
Systolic Blood Pressure (mmHg)	Admission	91 ± 16	85 ± 15	0.274
	24-hour	103 ± 16	-	
	p-value **	0.022		
	48-hour	106 ± 13	-	
	p-value	0.007		
	72-hour	114 ± 21	-	
	p-value	<0.001		
Diastolic Blood Pressure (mmHg)	Admission	64 ± 11	57 ± 12	0.074
	24-hour	66 ± 15	-	
	p-value	0.560		
	48-hour	64 ± 16	-	
	p-value	0.680		
	72-hour	65 ± 14	-	
	p-value	0.750		

All values shown as mean ± standard deviation.
* p-values representing the difference between case and control groups
**p-values representing the difference between admission and mentioned time.

Table 1. The demographic and clinical features of the participants by the total and case and control groups. **

	Total	Groups		P value*
		Case	Control	
Age (Year)	28 ± 11	27 ± 10	32 ± 14	0.122
Sex				0.854
– Male	44 (57.9%)	35 (57.4%)	9 (60.0%)	
– Female	32 (42.1%)	26 (42.6%)	6 (40.0%)	
The use AlP tablet with water				0.579
– No	72 (94.7%)	57 (93.4%)	15 (100.0%)	
– Yes	4 (5.3%)	4 (6.6%)	0 (0.0%)	
Number of AlP tablet	3 ± 2	3 ± 2	3 ± 2	0.486
Vomiting after exposure				0.073
– No	25 (32.9%)	17 (27.9%)	8 (53.3%)	
– Yes	51 (67.1%)	44 (72.1%)	7 (46.7%)	
Transfer time to hospital	2.6 ± 2.6	2.6 ± 2.7	2.4 ± 2	0.821
Heart Rate (Beat/minute)	94 ± 22	93 ± 21	99 ± 27	0.311†

AlP: aluminum phosphide
*p-values for the different between case and control groups.
** values are shown as mean ± standard deviation for continuous variables and number (%) for categorical variables.

the average arterial pH in both groups remained consistent with the initial values. During hospitalization, significant increases were noted in the mean values of PaCO2, Bicarbonate, and Base Excess (BE) in the case group.

Notably, a substantial proportion of patients (72.4%) necessitated intubation, with the treatment group displaying a 10% lower incidence of intubation than the control group, although this difference did not reach statistical significance. However, the mean intubation duration in the case and control groups differed significantly, with durations of 70 ± 74 and 27 ± 15 minutes, respectively (p-value: 0.041). Furthermore, when comparing deceased and surviving

Table 3. Comparison of the initial and last arterial blood gas test in patients with acute poisoning by ALP in the Case and control groups.

		Case	Control	P-value*
pH	Admission	7.27 ± 0.17	7.18 ± 0.18	0.072
	Last day	7.26 ± 0.2	7.15 ± 0.19	0.276
	P-value **	0.985	0.69	
PaCO2	Admission	34.52 ± 13.86	36.91 ± 11.9	0.543
	Last day	43.43 ± 11.22	52.26 ± 23.86	0.081
	P-value	<0.001	0.092	
HCO3	Admission	15.44 ± 5.71	13.51 ± 3.45	0.213
	Last day	20.84 ± 7.44	19.38 ± 10.74	0.615
	P-value	<0.001	0.13	
Base Excess (BE)	Admission	-9.12 ± 8.4	-10.13 ± 11.31	0.701
	Last day	-5.85 ± 10.06	-9.68 ± 11.02	0.596
	P-value	0.03	0.305	

All values shown as mean ± standard deviation.
* p-values representing the difference between case and control groups
**p-values representing the difference between admission and mentioned time.

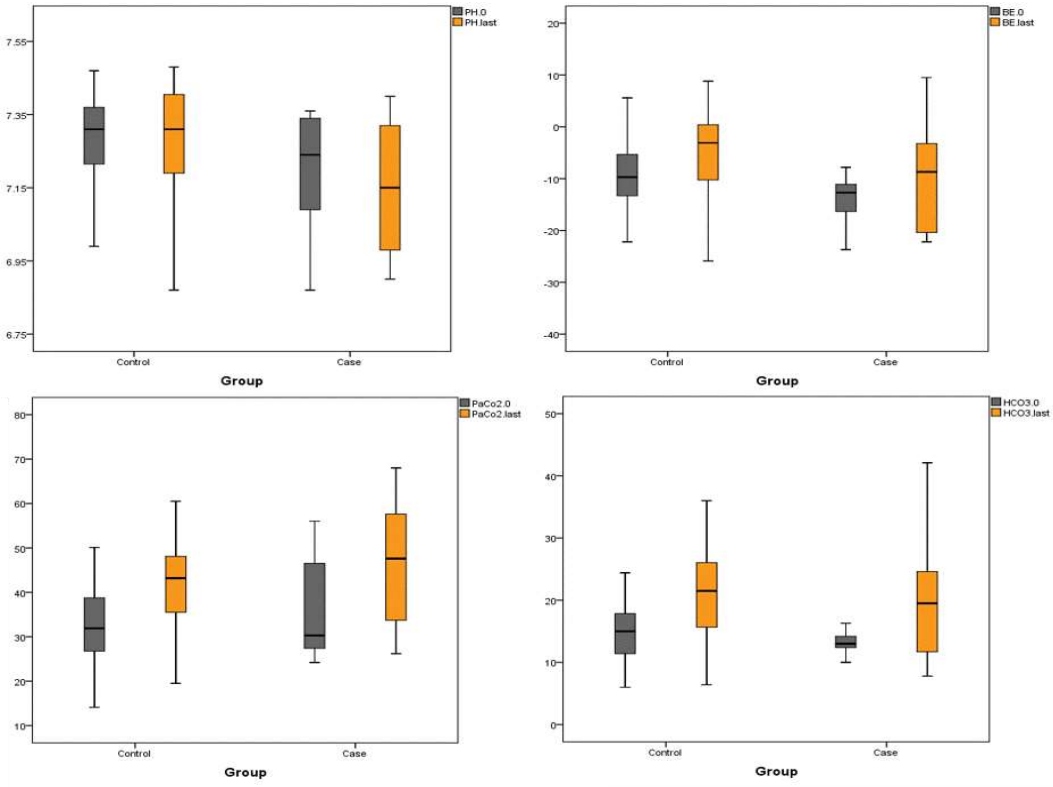

Figure 1. The mean ABG parameters in case and control groups.

patients within these groups, the treatment group exhibited a significantly longer mean duration of hospitalization than the control group.

In terms of mortality, 50 deaths were reported, with 37 (60.7%) occurring in the treatment group and 13 (86.7%) in the control group, marking marginally significant differences (P-value: 0.058). Further insights into the details of mortality within the case and control groups are presented in Table 4 and Figure 2.

Table 4. Comparison of mortality in patients with acute poisoning by AlP in the control and case groups

	Total	Group		P-value
		Case	Control	
Death	50 (65.8%)	37 (60.7%)	13 (86.7%)	0.058

AlP: aluminum phosphide
*p-values for the different between case and control groups.

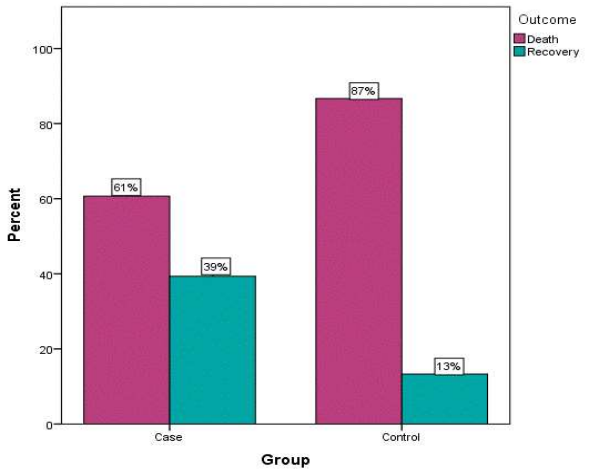

Figure 2. Mortality in case and control groups

DISCUSSION

This study investigated the mortality and safety of HIE therapy in 76 patients with AlP toxicity with an average age of 28. The mortality rate in the HIE group was 26% lower than in the control group (p-value: 0.058). Besides, this research detected a significant rise in systolic blood pressure during hospitalization in the treatment group. Regarding pH and bicarbonate levels, the HIE group showed less metabolic acidosis. In contrast to the case group, the therapy group's bicarbonate levels significantly increased throughout hospitalization.

In a smaller population trial, Pannu et al. [1] discovered that HIE increases survival, length of hospitalization, and blood pressure while decreasing the requirement for ventilation in AlP poisoning. Similarly, another research at Loghman Hakim Hospital confirmed this study's findings, although with a more negligible effect [5]. In this study, patients in two groups of 44 people, control and treatment, in addition to receiving conventional treatments, were treated with glucose, insulin, and potassium in the treatment group. This study's results suggest that the duration of hospitalization and discharge, i.e., the survival rate, was significantly higher in the treatment group. More research on a larger scale on the therapeutic effects of HIE is required to demonstrate the efficacy of this approach.

GIK was first introduced for treating acute poisoning with beta-blockers and calcium channel blockers [7]. Further investigation suggested that insulin can be helpful in any poisoning that causes hemodynamic instability [8]. Vasodilatory and inotropic effects of insulin are well established [9,10]. Combining these actions increases cardiac output, which is further improved by enhancing ventricular relaxation. Numerous types of cardiogenic shock are characterized by microcirculatory dysfunction, which causes heterogeneous blood flow at the distal arteriole and capillary level and tissue ischemia [11]. At the level of the terminal arteriole and capillary, insulin has also been found to improve microvascular recruitment (blood flow becoming less heterogeneous), an action most likely caused by an increase in nitric oxide generation. Capillary flow can achieve perfusion densities comparable to those of working muscles [10]. This study aimed to emphasize the significance of the insulin impact by downplaying the significance of other therapies, even though the effect of employing vasopressors in such poisonings is uncertain in comparable studies [12]. This study recommends further investigations to discover more about the pathophysiology of insulin in aluminum phosphide poisoning,.

The current study revealed that HIE raises SBP by 25%, consistent with previous reports [13-15]. The cause of these patients' low blood pressure could be a cardiogenic shock, shock caused by circulatory failure, or both [16]. Increased vessel permeability can be mentioned, among other factors, due to wall cell damage and the outbreak of toxicity in cardinal cells [16].

The present study found that patients had abnormalities in their arterial blood gases and metabolic acidosis, consistent with previous findings [17]. A significant difference was found in the relative pressure of CO2 in the blood in the treatment group between the start and end of treatment, which could indicate medical procedures (prescription of sodium bicarbonate) or compensatory activities of the body to regulate metabolic acidosis [14]. According to other studies, the decrease in serum bicarbonate value less than 20 mEq/L could be related to metabolic acidosis brought on by severely toxic exposure to aluminum phosphide. Nevertheless, interestingly, the current study found a substantial correlation between the patient's HCO3 value at the beginning and end of the study, which may have contributed to the regulation of metabolic acidosis in poison victims receiving large doses of insulin [18]. Indicatively, base Excess (BE) could be more accurate for interpreting acidosis and alkalosis with a metabolic origin than bicarbonate ion analysis. According to the BE value reported in this study, which is less than (-2), the presence of metabolic acid in AlP patients is confirmed. However, the value of BE at the start and end date in the treatment group is notably significantly different, indicating improvement in metabolic acidosis in patients undergoing

HIE treatment.

LIMITATIONS

This study boasts several robust strengths that contribute to its significance. It encompasses a relatively large cohort of individuals afflicted with AlP toxicity, which is often a challenging condition to investigate due to its relative rarity. The randomized allocation of participants into treatment and control groups enhances the internal validity of the findings, while the incorporation of comprehensive demographic and clinical data fortifies the depth and reliability of the study. The research's meticulous focus on critical clinical parameters, including systolic blood pressure and arterial pH, provides a comprehensive understanding of the impacts of Hyper Insulin Euglycemia (HIE) therapy in AlP poisoning cases, offering invaluable insights into treatment dynamics. Moreover, the study's emphasis on bicarbonate levels and metabolic acidosis significantly advances our comprehension of the metabolic consequences of the therapy. The report of a marginally significant difference in mortality rates (p-value: 0.058) underscores the potential benefits of HIE therapy in the context of AlP poisoning. By delving into the role of insulin in cases characterized by circulatory failure and cardiogenic shock, the study contributes to our understanding of insulin's pathophysiological mechanisms, enriching our knowledge of its actions in these specific poisoning scenarios.

Nonetheless, the study is not without limitations. One key constraint lies in the relatively modest sample size, which could affect the generalizability of the findings. The retrospective nature of data collection introduces potential selection bias and uncontrolled confounding variables, which may have influenced the results. Additionally, the marginally significant difference in mortality rates between the treatment and control groups (p-value: 0.058) highlights the necessity for larger-scale, prospective investigations to definitively ascertain the effectiveness of HIE therapy in AlP poisoning cases. The study primarily concentrates on short-term outcomes, and the absence of long-term follow-up data restricts the assessment of sustained effects and patient outcomes. Addressing these limitations by conducting larger prospective studies with extended follow-up periods is vital to provide a more comprehensive understanding of the efficacy and safety of HIE therapy in AlP poisoning cases and to refine our comprehension of this intricate medical challenge.

CONCLUSION

Using the HIE protocol accompanied by Symptomatic and supportive treatments in acute ALP toxicity in the case group of this study resulted in a significant increase in systolic blood pressure and longer survival time. Although no significant differences were observed in laboratory testing results and intubation needs among case and control groups of this study, death rate differences among these two groups show a promising way for ALP toxicity treatment.

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