ORIGINAL ARTICLE

Triiodothyronine Mitigates Cardiac Dysfunction in Aluminum Phosphide Poisoning: Findings from a Randomized Clinical Trial

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Abstract

Introduction: Aluminum phosphide (AlP) poisoning, commonly known as rice tablet poisoning, is a lethal method of suicide with no known antidotes. Thyroid hormones have inotropic effects that can potentially reverse hemodynamic instability and improve cardiac output. This study investigated the effects of Triiodothyronine (T3) on the cardiac function of patients with aluminum phosphide poisoning.
Methods: In this randomized clinical trial, 24 patients with confirmed ALP poisoning were recruited. The intervention group received T3 treatment in addition to standard treatment, while the control group received only standard treatment. Demographic variables, cardiac parameters, biochemical markers, and oxidative stress tests were evaluated.
Results: The majority of participants were men (60%) in their thirties (intervention: 32±17.4 years; control: 30±11.6 years). Following treatment, both systolic and diastolic blood pressures had significantly higher mean differences in the T3 group compared to the control group (18.7±9.3, P=0.05 and 14.1±5.9, P=0.03 respectively). While both groups showed improvement in mean arterial pH, the intervention group exhibited a significantly greater improvement 12 hours after the administration of T3, which was significantly different from both the baseline and control groups (p=0.04, 0.009 respectively). Additionally, the intervention group had a lower QRS and QTc interval compared to admission time.
Conclusion: Triiodothyronine administration has been shown to maintain a higher range of SBP, control cardiogenic shock, regulate metabolism, improve acidosis and blood pressure, and ultimately enhance recovery in patients with aluminum phosphide poisoning. Furthermore, it may have cardio-protective effects on these patients.

Keywords: Aluminum Phosphide, Phosphine, Poisoning**,** Triiodothyronine

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INTRODUCTION

Chemical compounds, including rodenticides and fumigants, are commonly used as pesticides globally to protect agricultural products from insects and rodents. While some of these chemicals are only mildly toxic, highly toxic compounds like metal phosphide rodenticides (which contain aluminum, zinc, or magnesium) can cause severe poisonings [1,2,3].

Pesticide poisoning can occur by accident, intention, occupation, or even as an act of suicide. This type of poisoning is a global health issue, claiming the lives of around 300,000 people annually [1]. Metal phosphides, such as aluminum phosphide are commonly used in many countries as rodenticides and insecticides. Aluminum phosphide (AlP) produces a poisonous gas called Phosphine (PH3) when exposed to moisture or gastric acidity, absorption of phosphine gas through the gastrointestinal tract and lungs inhibits cytochrome-c oxidase enzyme and oxidative phosphorylation resulting in adenosine triphosphate depletion and cell death [2,3,4]. The most clinical disturbances induced by AlP are arrhythmias, congestive heart failure, refractory hypotension, tissue hypoperfusion, pulmonary edema, refractory metabolic acidosis, acute renal failure, and in developed stages multiple organ system failure [2, 4,5].

AlP poisoning induces several ECG abnormalities such as ST alterations, QRS widening, prolongation of the QTC interval that are correlated closely with later development of the complications and mortality rate of acute AlP poisoning [1,6].

The incidence of poisoning and mortality rate of ALP poisoning in some Asian and developing countries like Iran is high, and efforts to reduce its incidence and improve treatment outcomes are needed [7,8]. Evidence from the Forensic Medicine Facility of Iran indicates a high number of

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deaths related to ALP poisoning. Additionally, the results of a meta-analysis about AlP poisoning mortality rates revealed that the mortality rate for AlP poisoning was 27%, with a higher incidence in men than in women [7].

Currently, there are no specific antidotes or treatments available for AlP poisoning, despite its significant toxicity and high mortality rate. Some chemical and herbal treatments have shown promising effects in clinical or experimental studies for AlP poisoning. These include Vitamin E, N-acetyl cysteine (NAC), L-carnitine, magnesium sulfate, melatonin, triiodothyronine (T3), and glucagon [4,5, 6,9,10]. Triiodothyronine (T3) is a thyroid hormone that has long been used to treat hypothyroidism that evidences showed that intravenous injection of T3 in patients with advanced congestive heart failure can improve cardiac function and reduce arterial vascular resistance, due to the inotropic effects of thyroid hormones [11,12].

Evidences in animal studies, and some in human studies reported T3 administration is effective in controlling AlP poisoning and can improve patients' outcome [4, 12, 13]. The use of thyroid hormones in controlling and treating AlP poisoning is mainly attributed to their cytoprotective and antioxidant effects, as well as their ability to improve blood pressure and acidosis, as reported in studies [4, 12, 13].

The aim of this study was to examine the potential benefits of T3 treatment in enhancing the cardiac function of patients with AlP poisoning.

METHODS

Study Design and Patients

This study is a randomized, not blinded, case-controlled clinical trial on acute AlP-poisoned patients, who admitted during the first 3 h after onset of poisoning to the intensive care unit (ICU) of the Toxicology Emergency Room of Imam Reza Hospital in Mashhad, Iran. To be included in the study, the patients admitted to the ICU had to meet the following criteria: a documented history and clinical symptoms of acute aluminum phosphide (AlP) poisoning, ingestion of rice tablets up to three hours before hospital admission, and positive test results for silver nitrate (AgNO3) in gastric aspirate, with systolic blood pressure less than 100 mmHg, cardiogenic shock, and acidosis. Individuals with a negative silver nitrate spot test, pre-existing heart disease, or who consumed herbal rice tablets (also known as garlic tablets), acute myocardial infarction, thyroid diseases, adrenal insufficiency, or hypersensitivity to T3, were excluded from the study.

Sample size was determined based on the relative simple study regard to difference of blood pressure with alpha 0.5 and power 80% [13]. A total of 24 patients were enrolled in the trial and randomly assigned to two groups: the intervention (T3) group and the control group, with 12 patients in each. As the control group did not receive a placebo administration, this study was conducted in an open-label manner. Both groups received the standard treatment protocol, which included gastric decontamination with potassium permanganate solution (1:10,000) and then sodium bicarbonate gavage (100 mEq), fluid therapy, sodium bicarbonate (1-2 mEq/kg, IV, and then every 8 h), proton pump inhibitor (Pantoprazole, 40 mg, IV stat and every 12h), magnesium sulfate (2 g stat, and every 6 h, IV infusion), norepinephrine (2-4 mcg/min, if SBP< 90 mmHg), N-acetyl cysteine (NAC) (dose as per antidote therapy in Acetaminophen poisoning)[13]. The intervention group in this study received a starting dose of 75 micrograms of T3 via nasogastric tube after gastric lavage, followed by 25 micrograms of T3 every 8 hours for three consecutive doses. The first dose was administered concurrently with sodium bicarbonate gavage. Patients in both the intervention and control groups were closely monitored until discharge or death to assess the safety and efficacy of the treatment.

Demographic Variables

Data were collected from the patients, including age, sex, place of residence (rural or urban area), suicide attempt, and location of purchase of rice tablet (pesticide store, apothecary).

Cardiac Variables

In the study, various cardiac variables were evaluated, including the use of serial electrocardiogram (ECG) monitoring to assess electrocardiographic parameters such as heart rate, the QRS interval, heart rate-corrected QT interval (QTc interval), and the presence of arrhythmia. Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP). Blood pressure (BP) was measured on the right arm of each participant upon admission to the hospital, and then every half hour while in a supine position, with measurements recorded in millimeters of mercury. Consider a wide QRS complex if the QRS duration is greater than or equal to 120 milliseconds and a prolonged QTc interval if it exceeds 450 msec, normal values for the QTc range from 350 to 450 msec for adult men and from 360 to 460 msec for adult women [2]. The QTc interval is an important ECG parameter that reflects the duration of ventricular depolarization and repolarization. It is commonly used to assess the risk of arrhythmias. There is a graded relationship between QTc interval prolongation and the risk of cardiac mortality and sudden death, which we evaluated in our study [14]. Data of Cardiac variables after the first 12 hours of admission were assessed and compared between two groups.

Biochemical Tests

A set of biochemical tests were performed on two groups of individuals at baseline and 12 hours after treatment. Biochemical tests included arterial blood gases (ABGs), liver function tests (such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, and direct bilirubin), coagulation tests (including Prothrombin Time (PT), International Normalized Ratio (INR), and Partial thromboplastin time (PTT)), creatine phosphokinase (CPK), and blood sugar (BS). Venous blood was collected from both groups to assess study variables, while arterial blood was collected from the radial artery in both groups using a pre-heparinized syringe.

Oxidative Stress Tests

1) ***Malondialdehyde (MDA) Level***

To measure the levels of malondialdehyde (MDA), 2.5 ml of

venous blood samples were collected from each patient in the intervention group following T3 administration. In the process of lipid peroxidation, MDA is produced and reacts with thiobarbituric acid (TBA) to yield the MDA-TBA complex. MDA results were expressed in micromole per liter (mmol/L).

2) Superoxide dismutase (SOD) activity

To measure the levels of SOD, 2.5 ml of venous blood samples were collected from each patient in the intervention group following T3 administration. Serum SOD activity was measured using the Nasdox™ assay kit according to the manufacturer's instructions. Samples were prepared, and their absorbance was read at 440-460 nm. The activities were reported as units per milliliter (U/mL).

Patients' Outcome

The final outcome was assessed using mortality (survival) rate. The mortality (survival) rate is an important endpoint in clinical research, providing valuable information about the effectiveness of a treatment or intervention in improving patient outcomes.

Ethics

This study was approved by the Ethics Committee of Mashhad University of Medical Sciences, Iran, with the code number ir.mums.fm.rec.1396.165 and registered in the Iranian Registry of Clinical Trials with the code number IRCT20130811014330N8. Written consent was obtained from all individuals or their legal guardians to participate in this study, and their personal information, including their name, was kept confidential. Every patient was given a project code, and the data were analyzed accordingly. The raw data were kept by the lead investigator.

Statistical Analysis

The collected data were analyzed using IBM SPSS Statistics for Windows, version 25. Quantitative data were reported as means and standard deviations (SD) or medians and interquartile ranges (IQR), while qualitative data were reported as percentages. Independent samples T-tests, Mann-Whitney, Chi-square tests, and Fisher's exact tests were used to compare variables between the intervention and control groups. A significance level of less than 0.05 ($P < 0.05$) was considered statistically significant for all tests.

RESULTS

Demographic Description

Of the participants, 60% were male, and there was no significant difference in sex distribution between the intervention and control groups (P=0.51). Most participants in both groups were in their 30s, with mean ages of 32±17.43 years and 30±11.61 years for the intervention and control groups, respectively. The difference in age between the two groups was not statistically significant (P=0.84). The history of suicide attempts was also similar between the two groups (P=0.76), the primary source of rice tablets was an apothecary for both groups (P=0.66) and almost of the participants lived in urban areas (P=0.06). Table 1 provides a detailed breakdown of the demographic characteristics of the participants.

Cardiac Results

At baseline, the SBP and DBP measurements were similar in both the case and control groups, with no significant differences observed (92.1 ± 4.9 and 48.1 ± 4.1, respectively, P=0.72 and 0.91). However, after treatment, a statistically significant difference was observed between the two groups, with the intervention group that received T3 having significantly higher SBP and DBP compared to the control group (P=0.03 and 0.01, respectively). No significant differences were observed between the intervention and control groups in other cardiac variables, such as heart rate, QTc, and QRS interval ($P > 0.05$). Also, cardiac arrhythmias, there were slightly fewer incidences in the intervention group compared to the control group, but this difference was not statistically significant (P=0.66). Table 2 presents a comparison of the cardiac parameters of the study participants after treatment.

Biochemical Results

The results of arterial blood pH in both the case and control groups at the admission (baseline) were similar (7.1 ± 0.1, 7.1 ± 0.2, respectively, P=0.94), after treatment there was shown a remarkable difference in the mean of arterial pH, which was 7.3± 0.1 in the intervention group and 7.1±

Table 1. Demographic variables of study participants.

Variable	Category	Intervention group Number (%)	Control group Number (%)	P-value*
Sex	Female	5 (41.7)	4 (33.3)	0.51
	Male	7 (58.3)	8 (66.7)	
Place of residence	Urban	11 (91.7)	6 (50.0)	0.06
	Rural	1 (8.3)	6 (50.0)	
Suicide attempt	Yes	1 (8.3)	1 (8.3)	0.76
	No	11 (91.7)	11 (91.7)	
Purchase location	Pesticide store	5 (41.7)	5 (41.7)	0.66
	Apothecary	7 (58.3)	7 (58.3)	

* Chi square or Fisher Exact Test

0.1 in the control group (P=0.009).

Arterial blood gases were analyzed in both groups, and the results showed no significant differences in the mean of PCO2 and HCO3 (P=0.26 and P=0.24, respectively).

The mean values of coagulation factors (PT/INR, PTT), hepatic transaminases (AST, ALT, ALP), Blood glucose and creatine phosphokinase levels were not significantly different between the two groups((P>0.5). It was observed a significant decrease in serum bilirubin levels in the intervention group compared to the control (P=0.005). Total and direct bilirubin in the intervention group were significantly lower than that of the control group (P=0.01, 0.005 respectively). Table 3 shows the comparison of Biochemical tests results of study participants after treatment.

Oxidative Stress Tests Results

The mean MDA level was 3.6±0.4 (mmol/L) and the mean SOD activity was 573.5±147.0 (U/ml), and there were no significant differences between the two groups (P=0.41 and 0.71 for MDA and SOD, respectively).

Patients' Outcome

In this survey, the total mortality rate was 33.3%. The intervention group had a higher survival rate of 75.0% compared to 58.3% in the control group, but the difference was not statistically significant (P=0.66). This lack of

Table 2. Comparison of cardiac parameters of intervention and control groups after treatment.

Variable		Intervention group (Mean± SD)	Control group (Mean± SD)	P-value*
Systolic Blood Pressure (mm Hg)		98.3±24.0	79.5±19.8	0.05
Diastolic Blood Pressure (mm Hg)		67.3±15.5	50.9 ± 11.3	0.03
Heart rate (bpm)[+]		106.8 ±24.9	93.2± 15.8	0.21
QRS interval (msec) [++]		99 ±25	93± 19	0.59
QTc interval (msec)		430± 47	426± 62	0.67
		Number (%)	Number (%)	P-value**
arrhythmias	Yes	3 (25.0)	5 (41.7)	0.66
	No	9 (75.0)	7 (58.3)	

*T-Test, ** Fisher Exact Test
[+]beats per minute [++]milliseconds

Table 3. Comparison of biochemical tests of intervention and control groups after treatment.

Biochemical Test		Intervention group (Mean ± SD)	Control group (Mean ± SD)	P-value*
pH		7.32± 0.1	7.15± 0.1	0.009
HCO3 (mmol/L)		19.07 ± 6.2	14.41 ± 5.9	0.09
PCO2 (mmHg)		32.4± 13.6	40.2± 12.9	0.66
PO2 (mmHg)		37.6 ± 8.5	35.9 ± 14.5	0.79
Blood glucose (mg/dL)		117.1 ± 34.9	165.7 ± 123.8	0.32
Coagulation Factors	PT (seconds)	15.2± 1.8	14.4± 2.2	0.35
	INR	1.40±0.3	1.2± 0.3	0.31
	PTT (seconds)	26.7 ±2.1	43.1 ± 48.2	0.47
Biochemical Test		Intervention group Median(IQR)	Control group Median(IQR)	P-value**
Hepatic Transaminases	AST (units/L)	20.5(26)	23.5(20.7)	0.34
	ALT (units/L)	18.5 (12.2)	27.5(33.7)	0.40
	ALP (units/L)	162(43.5)	150(73.2)	0.26
Direct Bilirubin (mg/dL)		0.20(0.17)	0.40(0.2)	0.01
Total Bilirubin (mg/ dL)		0.60(0.3)	1.25(0.4)	0.005
Creatine phosphokinase (CPK) (units/L)		188.5(421.5)	142.5(194.1)	0.16

*T-Test, ** Mann Whitney Test
IQR: Inter Quartile Range

significance may be related to the limited sample size of the study, which may have affected the statistical power to detect differences between the groups.

DISCUSSION

In this study, the levels of blood pressure and arterial pH showed significant improvements in the intervention group, revealing the effectiveness of T3 in this regard. Specifically, the mean SBP/DBP in the intervention group after T3 administration was 98/65 mmHg, while it was 79/50 mmHg in the control group. T3 administration resulted in normal arterial blood pH levels being maintained in the intervention group after 12 hours of prescription, with a significant difference in mean arterial blood pH compared to both the baseline of the group and the control group after 12 hours. The mean arterial pH was significantly higher in the intervention group compared to the control group

T3 was found to have cardio-protective effects in an animal model of acute AlP poisoning, with improved ECG and oxidative stress parameters, increased mitochondrial function and ATP levels, reduced apoptosis, and shortened QRS interval in the intervention group [4]. In a study of twenty-four ICU patients poisoned with AlP, oral liothyronine administration (50 μg/kg) 6 hours post-exposure resulted in significant improvements in systolic blood pressure and acidosis, reduced lipid peroxidation, and prevented the reduction of total antioxidant capacity. [13].

Although the ECG parameter did not show significant differences between the intervention and control groups in our study, the QRS and QTc interval was lower in the intervention group compared to admission time. This finding suggests that T3 administration may be an effective treatment option for AlP poisoning.

Furthermore, no significant differences were observed in further chemical laboratory tests, except for bilirubin, between the two groups in the present study. In addition, a statistically significant decrease in total and direct bilirubin levels in the T3 group was shown compared to the control group. As bilirubin and biliverdin reductase A (the enzyme that produces bilirubin) have antioxidant and cytoprotective properties, such significant bilirubin reduction in the T3 group may be attributed to this effect, but further investigations are required [15].

The present study demonstrated a higher survival rate in the intervention group (75.0%) compared to the control group (58.3%), yet the difference was not statistically significant. This finding is consistent with another study conducted in India that used a combination of coconut oil and magnesium sulfate to treat patients with AlP poisoning, which reported a survival rate of 42.0% with no significant difference between the intervention and control groups [5]. Another study investigating the effect of oral liothyronine on the mortality rate in AlP poisoning also found no statistically significant difference in mortality rate between the control and liothyronine groups (25.0% vs. 33.0% respectively) [13].

In light of the results obtained considering AlP poisoning, T3 administration has been proposed as a potential therapy based on its known effects on cardiac function and metabolism.

CONCLUSION

The results demonstrated that tridothyronine may be a promising treatment option for improving acidosis and increasing blood pressure in patients with AlP poisoning. Tridothyronine, as a synthetic thyroid hormone, plays a crucial role in regulating metabolism and generating energy, which can enhance the body's ability to recover from the toxic effects of aluminum phosphide.

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