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Acetyl-*L*-Carnitine effect on acute aluminum phosphide poisoning: A randomized control trial

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ABSTRACT: Aluminum phosphide (AlP) is a leading cause of pesticide poisoning worldwide, with the heart being the critical organ most affected by its toxic effects. This randomized controlled clinical trial aimed to evaluate the potential protective effects of acetyl-L-carnitine (ALC) against AlP poisoning. The study involved forty-four patients poisoned with aluminum phosphide, randomly allocated to either the intervention group, which received basic treatment along with a 1g infusion of ALC upon arrival at the hospital and every 8 hours thereafter, or the control group, which received basic treatment alone. The study assessed the association between demographic and poisoning-related factors and mortality during hospital stays in both groups. The results showed that the mortality rate was substantially lower in the ALC group (45.4%, n=10) compared to the non-ALC group (77.3%, n=17), but it was not significant (P = 0.06). Additionally, the length of hospital stay was significantly shorter for patients in the ALC group compared to those in the control group, and after therapeutic intervention, patients in the ALC group exhibited a statistically significant elevation in ejection fraction compared to the control group. Preliminary results suggest that ALC treatment alongside standard care might reduce mortality and hospital stay in AlP-poisoned patients, albeit without detectable side effects. However, these findings are initial and should be approached with caution. They are not definitive, and larger, more comprehensive studies are vital for confirming ALC's efficacy and safety in clinical practice. The potential benefits of ALC in managing AlP poisoning warrant further investigation before widespread clinical application.

KEYWORDS: Acetyl-L-Carnitine; Aluminum Phosphide; Poisoning; Toxicity.

1. INTRODUCTION

Pesticide poisoning is a global health challenge, responsible for an estimated 300,000 fatalities each year. The most lethal agents implicated in these poisonings are organophosphates and phosphides, notably aluminum phosphide (AlP) and zinc phosphide (Zn3P2) [1]. In the context of Iran, AlP is a prevalent insecticide safeguarding vital agricultural commodities such as rice and grains from pest infestation in both storage and transportation phases [2]. When AlP reacts with humidity in the air, food, or body, it produces

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phosphine (PH3), a colorless, highly toxic substance whose pesticidal effect is activated. The ease of use, high efficiency, and low cost of AlP have led to its widespread application. However, these attributes have also made AlP a common compound used for suicide [2-4]. In addition to intentional usage for suicide, AlP has caused numerous unintentional deaths and accidental poisonings. Poisoning typically occurs through inhalation (usually unintentional) or oral ingestion (usually intentional, with suicidal intent) [4]. While poisoning by inhalation is rarely fatal, ingestion can lead to highly fatal outcomes.

AlP poisoning can induce severe hypotension, heart failure, myocardial infarction, and various cardiac dysfunctions such as ventricular tachycardia, fibrillation, supraventricular tachycardia, atrial fibrillation, flutter, and sinus tachycardia within the first 3-6 hours post-ingestion [2-4]. Proposed biochemical mechanisms for phosphine toxicity include inhibition of cytochrome oxidase and induction of oxidative stress. Phosphine inhibits mitochondrial complex IV, i.e., cytochrome C oxidase, by reducing Fe3+ in the heme nucleus, thereby impairing the electron chain reaction and ultimately causing cell death. The inhibition rate of complex IV by phosphine is reported to be around 45%. Additionally, it inhibits complexes I and II at rates of 21-49% and 21-28%, respectively [5]. Phosphine also affects the activity of enzymes that catalyze the formation of reactive oxygen species (ROS). The inhibition of these enzymes, coupled with mitochondrial dysfunction and the reduction of Fe3+ to Fe2+, leads to excessive accumulation of ROS and hydroxyl ions, resulting in cellular damage and even death [5].

Acetyl-L-carnitine (ALC), the acetylated form of carnitine, is a natural substance produced by human cells. This compound is administered to individuals who are unable to properly metabolize carnitine from their diet. ALC serves as a substrate in reactions involving the transfer of acetyl groups, playing a critical role in the Krebs cycle and β-oxidation of fatty acids. It has been proposed that ALC enhances mitochondrial function, inhibits mitochondria-dependent apoptosis, and reduces intracellular ROS levels by affecting ROS-catalyzing enzymes. Additionally, ALC binds to Fe2+, leading to its deactivation [6].

Despite the availability of numerous therapeutic interventions for phosphine poisoning, none have conclusively shown sufficient efficacy. Consequently, the objective of this investigation is to evaluate the potential efficacy of ALC administration as a therapeutic modality for AlP poisoning.

2. RESULTS

Table 1 offers an overview of the baseline characteristics and clinical outcomes of participants in the study, focusing on both those receiving L-carnitine infusion and those not. This table is instrumental in evaluating a wide range of variables, including bicarbonate, carbon dioxide, base excess, systolic blood pressure (SBP), diastolic blood pressure (DBP), blood pH, pulse rate, alongside key demographics, and clinical outcomes such as age, vital signs, blood chemistry parameters, gender distribution, ejection fraction, duration of hospitalization, and mortality rates. These parameters were assessed one hour following hospitalization, providing critical insights into the immediate impact of the medical interventions and patient conditions. Data within the table are meticulously presented, offering median values accompanied by interquartile ranges, and, where relevant, as numbers (percentages) to ensure a thorough and nuanced understanding of the study's findings.

The median ages, along with interquartile ranges (IQR), for the ALC and non-ALC groups were 32 (IQR: 14.75-49.25) and 34 (IQR: 27-41), respectively, providing a clear depiction of age distribution within each cohort. The proportion of male patients was 63.6% (n=14) in the ALC group and 77.3% (n=17) in the non-ALC group. No significant differences were observed in the fundamental characteristics between the two groups. However, the ALC group exhibited higher bicarbonate levels than the non-ALC group (19 (IQR: 9.05-28.95) vs 16.3 (IQR: 10.05-22.55)). Blood pH levels showed no significant disparities between the groups (7.31 (IQR: 7.17-7.45) vs 7.28 (IQR: 7.10-7.46)). In the ALC group, the quantity of glucose infused in patients was notably higher. The mortality rate in the ALC group was 45.4% (n=10), lower than in the non-ALC group, although this difference did not reach statistical significance, as indicated by a P-value of 0.068, with only trends observed. Post-treatment, the ejection fraction was significantly higher in the ALC group, and the duration of hospital stay, until discharge from the ICU or occurrence of death, was considerably shorter. A graphical representation of participants' flow within the study is essential in the following Figure1. This diagram methodically outlines the stages of recruitment, allocation, follow-up, and analysis. Specifically, it summarizes the initial cohort of eligible individuals, the subsequent enrollment of these individuals, and the distribution of subjects into the intervention arm (administration of L-carnitine) or control arm. Moreover, it presents the participants who completed the study in comparison to those who were excluded from the final analysis, due to a variety of factors, such as attrition or non-compliance with the study protocol.

Table 1. Baseline Characteristics and Outcome Comparison Between the Two Groups of Patients.

Variable		L-carnitine infusion		P-value
		Yes	No	
Baseline characteristics				
Age (years) MI		32 (17.25)	34 (7)	0.38[2]
Oxygen saturation (%) MI		97 (7.5)	96 (5.75)	0.26[2]
Pulse rate (beats per minute) MI		99 (20)	107 (35)	0.89[2]
SBP (mmHg) MI		100 (16.25)	90 (21.75)	0.08[2]
DBP (mmHg) MI		60 (24)	60 (16.5)	0.85[2]
pH MI		7.31 (0.14)	7.28 (0.18)	0.23[2]
Carbon dioxide (mmHg) MI		35.0 (10.10)	33.0 (19.4)	0.07[2]
Bicarbonate (mEq/L) MI		19.0 (9.95)	16.3 (6.25)	0.03*[2]
Base excess (mmol/L) MI		-7.90 (5.8)	-11.35 (7.8)	0.06[2]
Infused Glucose (grams) MI		111 (59.25)	75 (40)	0.02*[2]
Insulin (units) MI		110 (70)	120 (65)	0.95[2]
Gender NP	Male	14 (63.6)	17 (77.3)	0.33[1]
	Female	8 (36.4)	5 (22.7)	
Outcomes				
Ejection Fraction (%) MI		37.5 (29.8)	19 (17)	0.04*[2]
Hospitalization duration (hours) MI		19 (74)	48 (102)	0.03*[2]
Mortality NP	Alive	12 (54.45)	6 (27.3)	0.068[1]
	Dead	10 (45.55)	16 (72.7)	

* P-value < 0.05 was considered as statistically significant
1: based on Fisher's exact test, 2: based on Mann-Whitney U
MI: Median (inter quartile range), NP: Number (percent)
SBP: systolic blood pressure, DBP: diastolic blood pressure
Bicarbonate, carbon dioxide, base excess, systolic and diastolic blood pressure, blood pH, and pulse rate measurements of patients were assessed one hour after hospitalization.

Table 2 summarizes the outcomes of the Cox proportional hazards regression analysis, which assessed the relationship between mortality risk and several factors including gender, age, L-carnitine treatment, and post-treatment ejection fraction (EF). This analysis aimed to evaluate the association of these variables with the risk of mortality. According to the findings, male gender was observed to have an increased hazard for mortality (Hazard Ratio [HR]: 1.544), though this association did not attain statistical significance (95% CI: 0.613-3.888, p=0.356), indicating a potential but not confirmed risk factor. The table delineates the analysis focusing on these crucial aspects, notably including the impact of L-carnitine usage and ejection fraction after 12 hours, thereby offering insight into the dynamic interplay of gender, age, treatment interventions, and physiological responses in influencing mortality risk.

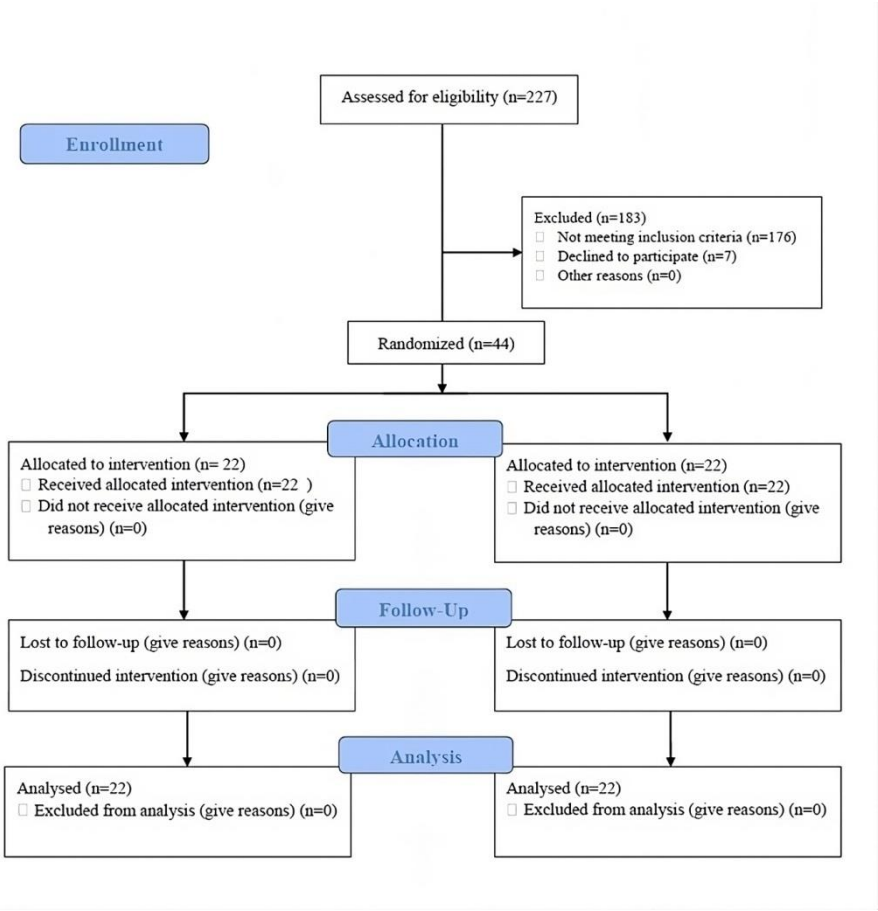

Figure 1. Participants' Flow diagram

Age demonstrated a slightly inverse relationship with mortality risk, indicated by an adjusted HR of 0.997 per year increase. The narrow confidence interval (95% CI: 0.957-1.039) and a P-value of 0.874 suggest that age, in this cohort, did not significantly impact mortality risk.

Notably, the lack of L-carnitine administration was correlated with an increased risk of mortality (adjusted HR: 2.032). However, the statistical significance of this finding was not established (95% CI: 0.741-5.573, p=0.169), implying an uncertain role of L-carnitine in modulating mortality risk in this context.

The most significant finding from our analysis is the impact of ejection fraction post-treatment. Each percentage increase in ejection fraction after 12 hours was associated with a 5.5% reduction in the risk of mortality (adjusted HR: 0.945, p=0.006). The narrow confidence interval (95% CI: 0.908-0.984) reinforces the statistical robustness of this finding, suggesting a clinically relevant protective effect of improved cardiac function in reducing mortality risk.

Table 2. Cox Regression Analysis Outcomes Assessing Mortality Risk Factors

Factor	Coefficient (B)	P-value (Sig.)	Hazard Ratio (HR)	95% Confidence Interval (CI) for HR
Gender (Male)	0.434	0.356	1.544	0.613 - 3.888
Age (per year increase)	-0.003	0.874	0.997	0.957 - 1.039
L-carnitine (Non-use)	0.709	0.169	2.032	0.741 - 5.573
Ejection Fraction after 12 hours (per % increase)	-0.056	0.006	0.945	0.908 - 0.984

3. DISCUSSION

In this randomized clinical trial, we evaluated the efficacy of ALC in treating patients with AlP poisoning. Our findings corroborate the hypothesis that ALC's cellular-level antioxidant effects effectively improve the clinical outcomes for patients suffering from AlP poisoning, where oxidative stress is a primary

mechanism of toxicity. Several studies have explored the impacts of various antioxidants on AlP poisoning [7]. For instance, a study conducted by Baghaei et al. in 2016 reported that acetyl L-carnitine significantly reduced oxidative stress biomarkers in a rat model of aluminum phosphide poisoning, leading to increased ROS and plasma iron levels. Additionally, cytochrome oxidase activity increased, and cardiomyocyte apoptosis decreased [8]. Furthermore, the effects of ALC against AlP showed promise in a study conducted by Abu-El-Zahab et al., and its therapeutic antioxidant effects have been explored in poisonings involving substances like cadmium [9]. In the present study, ALC usage led to a 37.3% reduction in mortality rate. However, these findings were not statistically significant.

It is worth noting that different studies have reported varying outcomes, possibly due to differences in treatment regimens and other factors. For example, a study involving high-dosage N-acetylcysteine reported significant reductions in mortality rates [11]. Given the variable nature of AlP poisoning, where mortality within the first 24 hours can range from 35% to 91% [12], many unknown or unclear factors could introduce bias. We aimed to minimize these effects through rigorous subject selection and statistical treatment. Lastly, our findings indicate that ALC treatment significantly reduced the duration of patients' hospital stays, consistent with other studies [7].

Limitations of the Study:

The study's single-center design may limit the generalizability of the results, due to potential variations in patient demographics and treatment protocols across hospitals. The small group of forty-four patients limits statistical power, increasing the risk of Type II errors and the likelihood of overestimating the effect size, thereby compromising the reliability of the results. The absence of stratification in the randomization process could lead to imbalanced patient characteristics and potential bias. Focusing on immediate outcomes without long-term follow-up restricts understanding of the treatment's prolonged effects and side effects. Uncontrolled factors, including patient lifestyle and, more specifically, varying levels of aluminum phosphide exposure, pose a risk of residual confounding. As a pilot study, the findings are preliminary and not definitive for clinical practice changes. Dependence on secondary data sources may introduce inconsistencies due to non-standardized record-keeping. The non-normal distribution of data necessitated the use of less powerful non-parametric tests, limiting the range of statistical analyses; this, combined with a small sample size, adds to the risk of bias in multivariate Cox regression models. The handling of missing data through multiple imputation, based on the assumption of randomness, could lead to biased results if this assumption is incorrect. Moreover, the small group size raises the risk of overfitting in statistical models, particularly when adjusting for multiple confounders or in subgroup analyses, potentially affecting the findings' generalizability and predictive accuracy. In summary, these limitations necessitate a cautious interpretation of the results and highlight the need for more comprehensive research to validate the study's conclusions.

4. CONCLUSION

While our preliminary findings indicate a potential reduction in mortality rate and hospital stay duration in AlP-poisoned patients receiving adjuvant ALC treatment, with no detectable side effects observed, these results should be interpreted with considerable caution. It is important to emphasize that these are initial observations and not definitive evidence of efficacy. Extensive further research, particularly larger and more comprehensive studies, is crucial to reliably confirm the benefits and safety of ALC treatment in this context. At this stage, the findings should be viewed as tentative and not as a basis for clinical decision-making regarding the widespread use of ALC in AlP poisoning.

5. MATERIALS AND METHODS

5.1 Study design and patient management

This randomized clinical trial was conducted on patients poisoned with aluminum phosphide (AlP) who were admitted to Loghman Hospital in Tehran, Iran, between 2020 and 2021. Upon admission, patients were randomized using a simple randomization method facilitated by a web-based service (sealedenvelope.com). This method utilized a computer-generated random numbers table to assign patients to either the treatment or the control group with a 1:1 allocation ratio. The random allocation sequence was created by an independent statistician who had no clinical involvement in the trial. This approach ensured that the assignment of patients was completely random, and that each patient had an equal chance of being allocated to any of the study groups, thereby reducing selection bias. To maintain the unpredictability of the assignment, the sequence was concealed from the researchers enrolling participants, and the allocation was

revealed only after the enrolled participant completed all baseline assessments and it was time to assign the intervention. Each patient underwent a thorough medical assessment. Collected demographic data included sex, age, systolic blood pressure since hospital admission (SBP), diastolic blood pressure since hospital admission (DBP), pulse rate since hospital admission, the quantity of AlP ingested, and the time elapsed between consumption and arrival at the hospital. Demographic data were reviewed and confirmed by a second member of the research team to ensure accuracy and completeness.

All patients initially received gastric lavage with potassium permanganate. Arterial blood gas (ABG) analyses were performed upon arrival and daily thereafter. Blood pH, bicarbonate (HCO3-), carbon dioxide (CO2), and base excess (BE) levels were recorded. Standard operating procedures (SOPs) for ABG collection and analysis were followed, and all laboratory technicians conducting the analyses were blinded to patient group assignment to minimize analytical bias. The SOPs adhered to internationally recognized guidelines to ensure consistency and reliability of the results. If blood pH exceeded 7.30 and/or HCO3- was below 15, a bicarbonate solution was infused. Additionally, norepinephrine was administered if SBP fell below 90 mmHg. To standardize treatment across all patients, dosages were calculated using a body surface area (BSA) formula, and the response to treatment was monitored by an independent committee. Treatment adherence was ensured by training staff on protocol and conducting random checks of treatment administration records.

All patients were adequately hydrated, and their blood glucose levels were carefully monitored. A continuous intravenous regimen of insulin, glucose, and potassium (GIK protocol) was administered based on individual blood glucose levels. These interventions were administered by a team trained in the GIK protocol to ensure consistent treatment administration. Patients also received intravenous magnesium sulfate at 1g initially and every 6 hours thereafter, calcium gluconate 10% at 1g initially and every 4 hours, and N-acetyl cysteine at 150 mg/kg every 8 hours. All patients were admitted to the intensive care unit (ICU) where cardiac function was monitored via EKG and echocardiography within the first six hours of admission. The EKG and echocardiography results were recorded and assessed by a blinded investigator to prevent assessment bias.

In addition to the standard treatments, the experimental group received a 1g L-carnitine infusion upon arrival and every eight hours thereafter. This dose was determined based on previous research and expert consensus to be both safe and potentially efficacious. The L-carnitine and placebo (for the control group) were indistinguishable in appearance and packaging to maintain double-blinding. The placebo was a saline solution that matched the L-carnitine solution in color and consistency. Carnitine, which helps preserve muscle glycogen and promote fat oxidation, was administered to individuals unable to properly metabolize carnitine from their diet. At the conclusion of the hospital stay or upon death due to poisoning, data including the duration of admission, amounts of insulin and/or norepinephrine administered, recorded ejection fraction, and duration of intubation (if applicable) were extracted from patient records. An independent audit was conducted on the data collection process to ensure that the data extraction was not influenced by the study hypothesis, and to verify the accuracy of the recorded data.

5.2 Inclusion Criteria

In this study, we included individuals aged between 18 and 65 who had a confirmed case of oral Aluminum Phosphide (AlP) ingestion. The criteria for inclusion were strictly defined to encompass those who specifically ingested one tablet of AlP within a two-hour window prior to their admission to the healthcare facility. Furthermore, a positive result on the silver nitrate test was a prerequisite for inclusion in the study. The silver nitrate test was chosen due to its rapid turnaround time and acceptable sensitivity for detecting AlP in gastric contents. Eligibility criteria were verified by two separate clinicians to reduce the risk of improper inclusion or exclusion from the study.

5.3 Sample size

Sample size was calculated using G-Power software, version 3.1, considering an alpha error level of 5% and a power of 80%. The mortality rate was estimated at 80% for the control group and 40% for the intervention group [7]. These estimates were based on a review of previous literature and the hospital's own preliminary data. Interim analyses were planned and overseen by an independent statistics expert to ensure the study could be stopped early for efficacy, futility, or safety concerns. Interim analyses were conducted after half of the expected events had occurred, which did not result in any changes to the study protocol. The optimal sample size was determined to be 44 patients, with 22 patients in each group. An independent statistician performed the randomization process.

5.4 Ethical considerations

The study was conducted in accordance with good clinical practice guidelines developed by the International Council for Harmonization and was based on the approved trial protocol. The protocol was reviewed and approved by an independent ethics committee. The study was approved and registered by the Iranian Registry of Clinical Trials (IRCT) center (Registration Code: irct.ir as IRCT20210720051946N1). Informed consent forms were designed to be easily understandable, with no medical jargon, ensuring informed participation. The consent process was documented, and a witness was present for all consent procedures to further ensure the ethical integrity of the process. Written informed consent was obtained from each patient's family in accordance with the principles of the Helsinki Declaration.

5.5 Ethical guidelines

This study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (SBMU) and assigned the following Registration Code: IR.SBMU.RETECH.REC.1399.273. Written informed consent was obtained from each patient's family prior to participation in the clinical trial.

5.6 Data analyses

Data were analyzed using SPSS software, version 22. The normal distribution of variables was verified using the Kolmogorov-Smirnov test. Categorical variables were expressed as frequency and percentage. Due to non-normal distribution, continuous variables were reported as medians and interquartile ranges (IQR). For clarity, the IQRs were calculated as the 25th to the 75th percentile ranges. Mann-Whitney U and Chi-square/Fisher's exact tests were employed to compare continuous and categorical variables, respectively. Univariate (crude) and multivariate (adjusting for potential confounders identified a priori based on literature review and expert opinion) Cox regression models were used to assess the association of demographic and poisoning-related factors, as well as L-carnitine infusion, with mortality during the hospital stay. These results were reported as hazard ratios (HR) with a 95% confidence interval. A two-tailed $P \leq 0.05$ was considered statistically significant. Multiple imputation techniques were employed to handle missing data, using a chained equations approach with five imputations to ensure a robust estimate of missing data. Sensitivity analyses were conducted to assess the impact of missing data and the robustness of the study findings.

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