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Article

Antidotal effect of dihydroxyacetone in aluminum phosphide-intoxicated patients

Hossein Niknahad ^{a,b,*}, Reza Heidari ^a, Ali Jangjoo ^c, Vahidreza Asghari ^d, Marziyeh Rashedinia ^b

^a Pharmaceutical Sciences Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

^b Department of Pharmacology and Toxicology, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran

^c Department of Emergency Medicine, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

^d Shiraz-Serum Pharmaceutical Industry, Shiraz, Iran

*Corresponding Author: Hossein Niknahad (ORCID: <https://orcid.org/0000-0001-6211-5936>), Department of Pharmacology and Toxicology, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran; e-mail: niknahadh@sums.ac.ir.

Abstract: Background: Aluminum phosphide (AIP), also known as “rice tablet,” is widely used as an effective pesticide. However, AIP poisoning is a common cause of mortality in many countries, such as Iran. Unfortunately, there is no specific antidote for AIP toxicity to date. AIP releases phosphine gas when it is exposed to moisture and acid. Phosphine is a robust mitochondrial toxin that could significantly inhibit cellular energy metabolism. AIP poisoning is an emergency condition that needs instant and effective intervention. Dihydroxyacetone (DHA) is a simple saccharide used for several pharmacological as well as cosmetic purposes. Previously, we found that DHA could significantly prevent mitochondrial impairment induced by toxic agents such as cyanide and phosphine in various in vitro and in vivo experimental models. Methods: Hospitalized patients (n = 111) were evaluated for eligibility criteria. Among these patients, n = 35 cases were excluded due to incomplete data (n = 11) and suspicion of poisoning rather than AIP (n = 24). Meanwhile, n = 76 cases with confirmed AIP poisoning were included in the study. AIP-poisoned patients who did not receive DHA (n = 18) were used as the control group. Patients (n = 58) received at least one dose of DHA (500 ml of 5% DHA solution w/v, i.v.) in addition to routine treatment of AIP poisoning. Arterial blood gas (ABG), blood pH, bicarbonate levels, and other vital signs and biochemical measurements were monitored. Moreover, the mortality rate and time of hospitalization were evaluated in both DHA-treated (n = 58) and AIP-poisoned patients without DHA administration (n = 18). Several biomarkers were assessed before (upon hospitalization) and after DHA treatment. The routine tests for AIP-poisoned patients in this study were the measurement of electrolytes (K⁺ and Na⁺), WBC, RBC, hemoglobin, INR, carbonate (HCO₃), blood pH, PaCO₂, and PaO₂ and SGPT, SGOT, BUN, Cr. Results: Upon patients' admission, significant decreases in blood pH (acidosis), blood PaO₂, and HCO₃ levels were the hallmarks of AIP poisoning. It was found that DHA significantly alleviated biomarkers of AIP poisoning and tremendously enhanced patients' survival rate compared to patients treated based on hospital routine AIP poisoning protocols (no DHA). No significant adverse effects were evident in DHA-treated patients in the current study. Interpretation: These data suggest that parenteral DHA is a novel and effective antidote against AIP poisoning.

Keywords: Aluminum phosphide; Clinical Toxicology; Dihydroxyacetone; Pharmacotherapy; Phosphine; Suicide; Toxicity

1. Introduction

Aluminum phosphide (AIP) is an effective pesticide for preserving stored grain, especially rice, from weevil damage.¹ AIP is known as the “rice tablet” in Iran and is widely used in Iran and some other countries, such as India, Thailand, Pakistan, *etc.*, to protect stored grains. However, acute and lethal toxicity is a common complication associated with AIP.¹ There is a concerning record of suicidal attempts using AIP in Iran.¹⁻⁶ Unfortunately, there is no efficient therapeutic intervention against AIP poisoning so far, and the mortality rate of this compound is very high (up to 80%).^{7,8}

AIP releases a significant amount of phosphine gas (PH₃) upon interacting with moisture or acids (*e.g.*, gastric HCl).⁹ Mechanistically, phosphine robustly impairs cellular energy metabolism. Phosphine inhibits the cytochrome *c* oxidase complex and consequently impairs mitochondrial ATP production.^{9,10} The phosphine-induced energy crisis is perilous for high energy-demanding organs such as the heart and brain,^{8,11,12}. However, many other complications and multi-organ failure could also occur in AIP toxicity, resulting in patient death.^{8,13,14}

AIP poisoning is an emergency state that requires immediate and rigorous therapeutic intervention. In addition to supportive care, previous studies suggested that the administration of olive/castor/coconut oils and antioxidant molecules such as N-acetyl cysteine, melatonin, vitamin C, and vitamin E are effective in the treatment of phosphine poisoning and significantly decreased AIP toxicity-associated complications.¹⁵⁻²² These interventions should be considered along with rigorous monitoring of vital signs, blood biochemistry, and brain/heart function. However, there is still a high mortality rate despite the treatment of AIP poisoning based on the mentioned routine protocols. The mortality rate of patients largely depends on many factors, including the amount of AIP ingested, time of admission to the hospital, concurrent poisoning with other agents, and the quality of therapeutic strategies and hospital care. Therefore, developing effective therapeutic options for managing AIP poisoning is critical.

Dihydroxyacetone (1, 3-dihydroxypropanone; DHA) is a simple saccharide freely soluble in water. DHA has been investigated for its pharmacological and cosmetic effects. It is used for skin tanning, increasing exercise capacity in athletes and the elderly, reducing weight, and mitigating the complications of fatty liver disease.²³⁻²⁸ Previously, we found that DHA is an effective antidote against the toxicity induced by lethal mitochondrial toxin cyanide in both *in vitro* and *in vivo* experiments.²⁹⁻³¹ It was found that DHA significantly improved mitochondrial function and prevented cellular ATP depletion during cyanide exposure.²⁹⁻³¹ In other *in vitro* and *in vivo* studies, we also found that DHA significantly prevented the toxicity induced by phosphine.³²⁻³⁴ It was found that DHA significantly prevented PH₃ cytotoxicity in cultured HePG2 cells and significantly decreased the mortality of phosphine-poisoned mice.³²⁻³⁴ Since DHA is produced in the body in the glycolysis pathway and is a very safe compound with an LD₅₀ of more than 8 g/kg in mice,³⁵ the current study was designed to evaluate the effect of DHA in AIP-poisoned human cases.

In some recent animal studies, it has been reported that oral DHA administration significantly decreased cardiovascular complications of AIP toxicity.³⁶ However, as AIP poisoning is an emergency state that rapidly deteriorates vital signs, a big challenge in managing AIP toxicity is the speed of delivering the protective agents to the body. On the other hand, it is preferred not to administer these agents by oral route in AIP poisoning because of its complications (*e.g.*, increasing the chance of phosphine gas release). Hence, the parenteral delivery of protective agents is ideal.

In the current study, patients with confirmed AIP poisoning received a parenteral formulation of DHA (at least one dose of 500 ml of 5% w: v of DHA solution, *i.v.*) in addition to systematic AIP poisoning treatment strategies. Several biomarkers and patients' survival were evaluated and compared with AIP-poisoned patients without DHA therapy. This data could pave the way to effectively treating AIP poisoning and decreasing the high mortality rate induced by this lethal toxin.

2. Methods

2.1 Dihydroxyacetone intravenous formulation

Dihydroxyacetone pharmaceutical-grade powder was purchased from Merck, Germany. It was formulated and prepared under sterile conditions as a 5% solution in 500 ml bottles by Shiraz Serum Pharmaceutical Company, Shiraz, Iran. The prepared DHA solution had all necessities of an intravenous formulation. Our laboratory studies showed that 2.6% solution of DHA is isotonic to the blood. The expiration date of the solution at room temperature (protected from light) was more than three years.

2.2 Study design and patients

This study enrolled patients aged 17-60 (male and female) diagnosed with confirmed ALP poisoning with significant blood acidosis, decreased PaO₂, and increased PaCO₂ in arterial blood gas analysis from October 2016 to December 2021. The study was conducted on patients referred to the Emergency wards of Shahid Faghihi, Aliasghar, and Nemazi Hospitals, Shiraz University of Medical Sciences, Shiraz, Iran, and Loghman and Maharlouie Hospitals, Tehran, Iran. Patients were excluded if there was an incomplete follow-up during hospitalization or suspicious poisoning with other agents rather than ALP. The flow chart for selecting patients for receiving DHA and standard routine treatments for ALP-poisoned patients is shown in Figure 1. In the primary assessment, n = 111 patients were evaluated for eligibility criteria. Among these patients, n = 35 cases were excluded due to incomplete data (n = 11) and suspicion of poisoning rather than ALP (n = 24). Meanwhile, n = 76 cases with confirmed ALP poisoning were included in the study. ALP-poisoned patients who did not receive DHA (n = 18) were used as the control group. Other patients (n = 58) received at least one dose of DHA (500 ml of 5% DHA solution w/v, i.v.) (Fig. 1). Arterial blood gas (ABG), blood pH, bicarbonate levels, and other vital signs and biochemical measurements were monitored. Moreover, the mortality rate and time of hospitalization were evaluated in both DHA-treated (n = 58) and ALP-poisoned patients without DHA administration (n = 18) (Fig. 1). Several biomarkers were assessed before (upon hospitalization) and after DHA treatment. The routine tests for ALP-poisoned patients in this study were the measurement of electrolytes (K⁺ and Na⁺), WBC, RBC, hemoglobin, INR, carbonate (HCO₃), blood pH, PaCO₂, and PaO₂ and SGPT, SGOT, BUN, Cr.

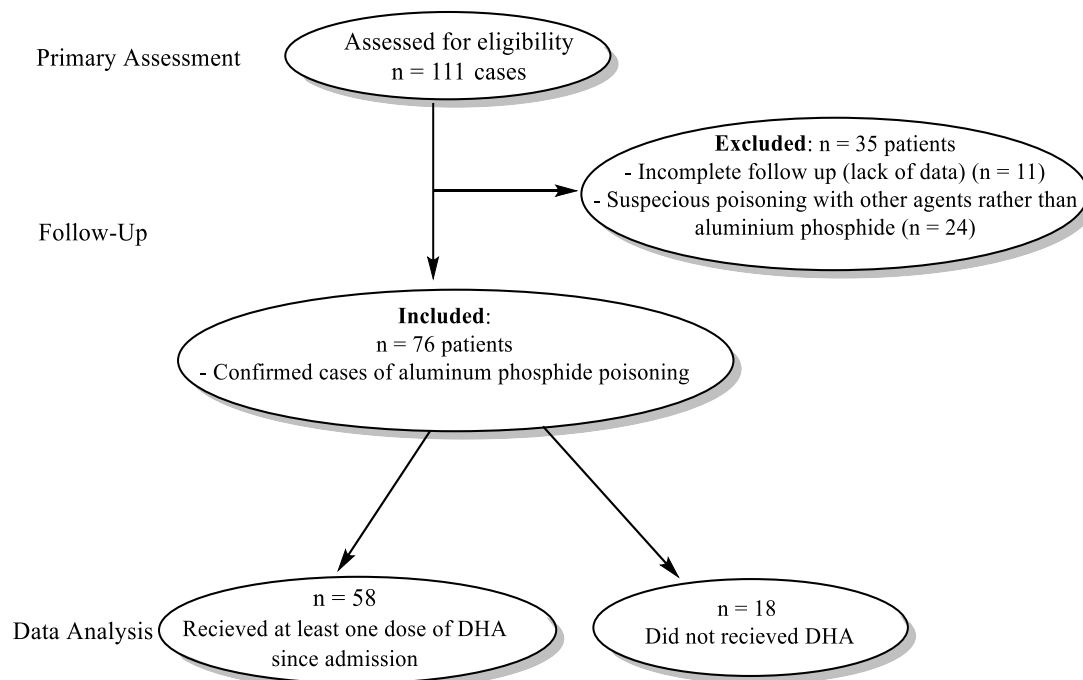


Figure 1. A flowchart of patient selection for evaluating the antidotal role of an intravenous formulation of dihydroxyacetone (DHA) in aluminum phosphide poisoned cases.

2.3. DHA Treatment Protocol

In addition to routine treatments for AIP poisoning (Fig. 2), the first 500 ml of 5% DHA was infused over 1 hour. Afterward, each 500 ml bottle was infused over 3 to 4 hours, if needed, till the patients' condition became normal. Usually, 2000 to 2500 ml of DHA was needed for each patient.

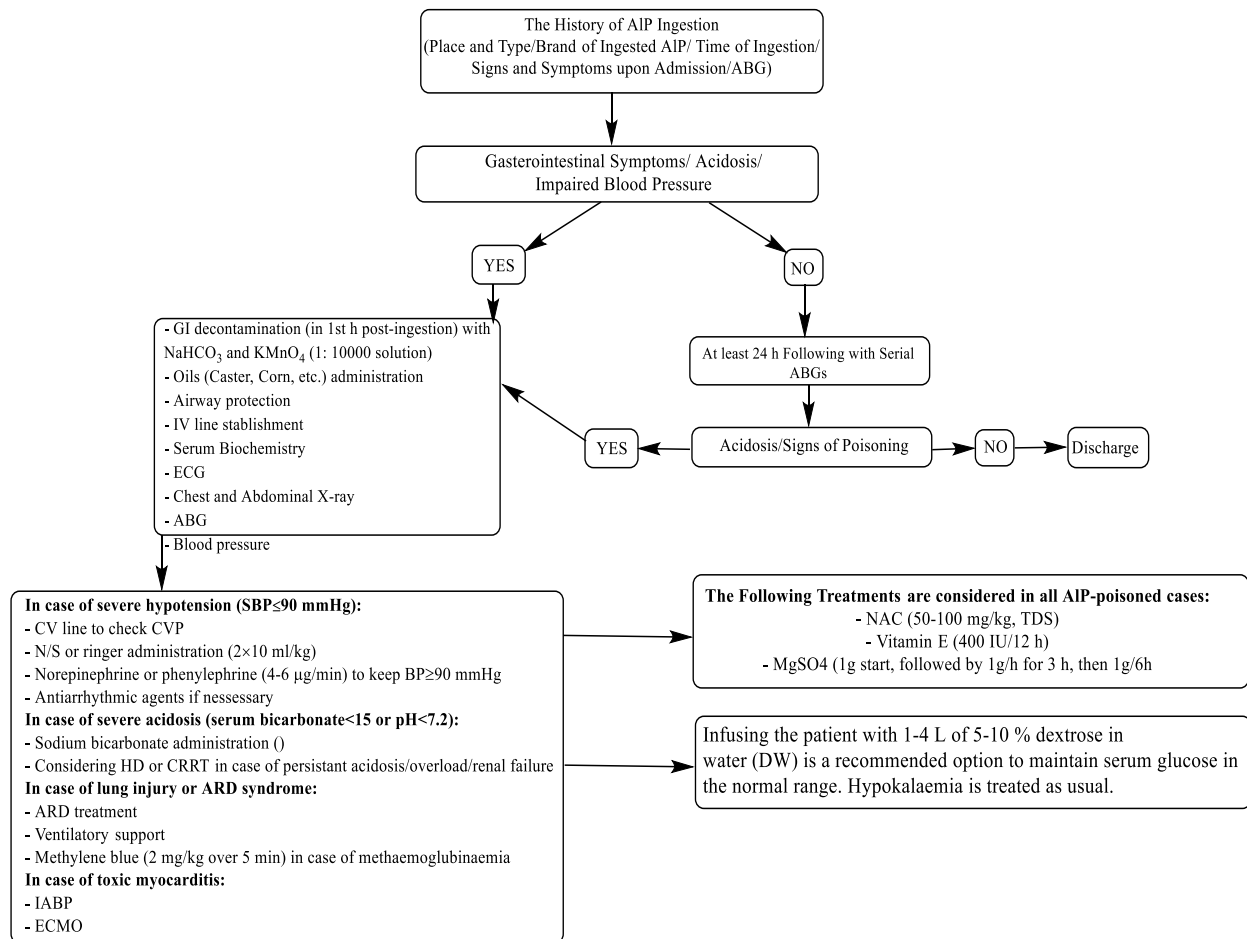


Figure 2. The flowchart of a standard aluminum phosphide (AIP) poisoning treatment procedure in hospitals is included in the current investigation. Intravenous dihydroxyacetone (DHA) was administered in addition to routine treatments in AIP-poisoned cases. SBP: Systolic blood pressure; N/S: Normal saline; CVP: Central venous pressure; ABG: Arterial blood gas; ECG: Electrocardiogram; CV: Central Vein; HD: hemodialysis; CRRT: Continuous renal replacement therapy; ARD: Acute respiratory distress; IABP: intra-aortic balloon pump; ECMO: Extracorporeal membrane oxygenation; DW: Dextrose water.

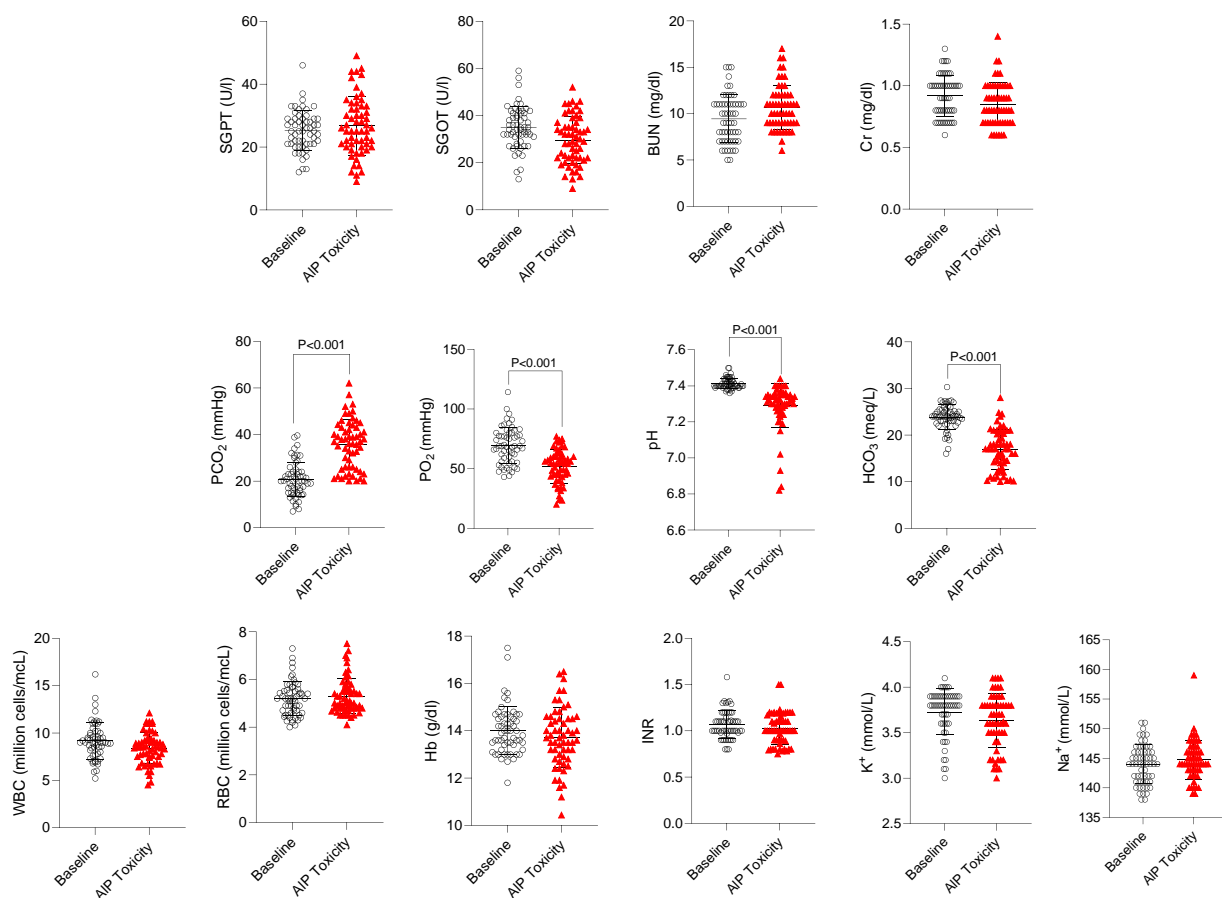
2.4. Statistical analysis

Data are represented as mean±SD. The data comparison for biomarkers assessed before and after DHA administration was carried out using a two-tailed student T-test. The data distribution for hospitalization time was not parametric, and the Wilcoxon test was used for data comparison.

3. Results

Several parameters, including biomarkers of organ injury (SGPT, SGOT, BUN, Cr), electrolytes (K⁺ and Na⁺), WBC, RBC, hemoglobin, INR, carbonate (HCO₃), blood pH, PaCO₂, and PaO₂ were assessed in confirmed cases of AIP-poisoned patients (n = 58) (Fig 2). No significant changes in biomarkers such as organ injury markers (SGPT, SGOT, BUN, Cr), CBC, hemoglobin, hematocrit, blood coagulation, and electrolytes were detected in AIP-intoxicated cases included in the current study (Fig 3). On the other hand, it was found that blood pH, PaO₂, and HCO₃ were significantly decreased, whereas PaCO₂

The mortality rate was another critical factor evaluated in DHA-treated patients and patients with routine AIP treatment protocols (Fig 6). It was found that DHA administration significantly decreased the mortality rate (about 67% in non-treated vs. about 35% in DHA-treated cases) (Fig 6). Although it was not statistically significant, the hospitalization time also tended to decrease in DHA-treated patients (Fig 6).



Data are represented as mean±SD.

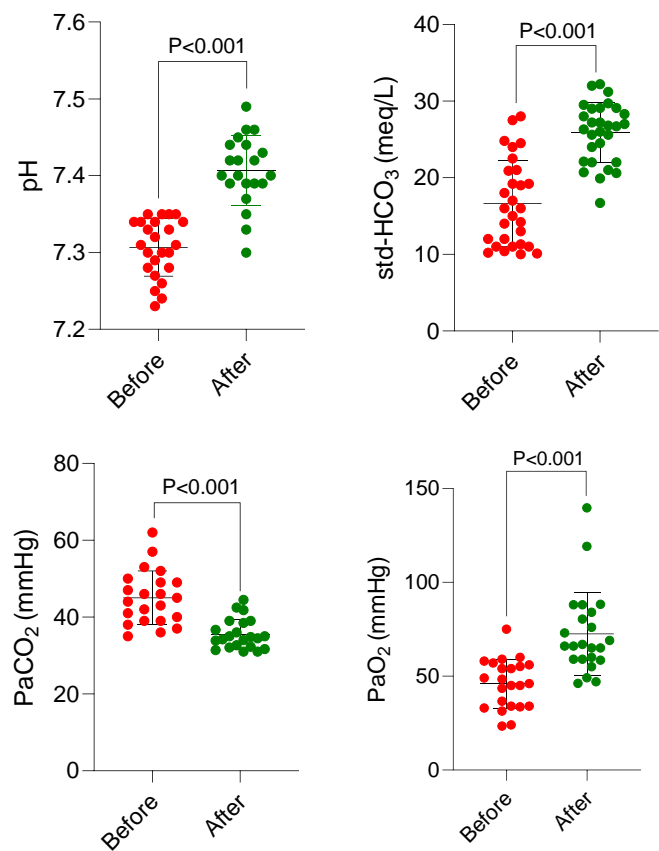


Figure 4. Arterial blood gases (ABG), bicarbonate (std-HCO₃), and blood pH as hallmarks of aluminum phosphide poisoning in patients before (upon admission) and after dihydroxyacetone (DHA) therapy and routine therapeutic protocols for AIP poisoning.

The data is represented as mean±SD. *Indicates a significant difference ($P < 0.05$).

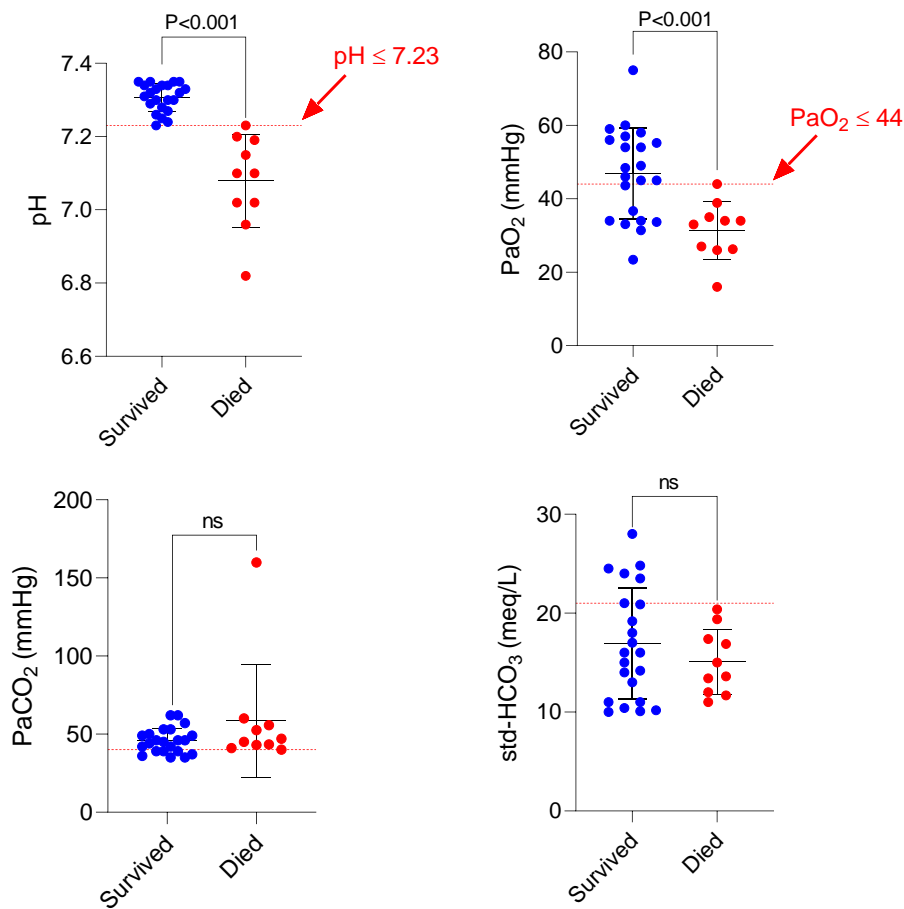


Figure 5. Factors related to poor prognosis in patients intoxicated with aluminum phosphide. Based on the data obtained in the current study, PaO₂ ≤ 44 and pH ≤ 7.23 could be considered risk factors for patient mortality. Patients with the mentioned criteria died despite dihydroxyacetone (DHA) administration and following other routine therapeutic protocols.

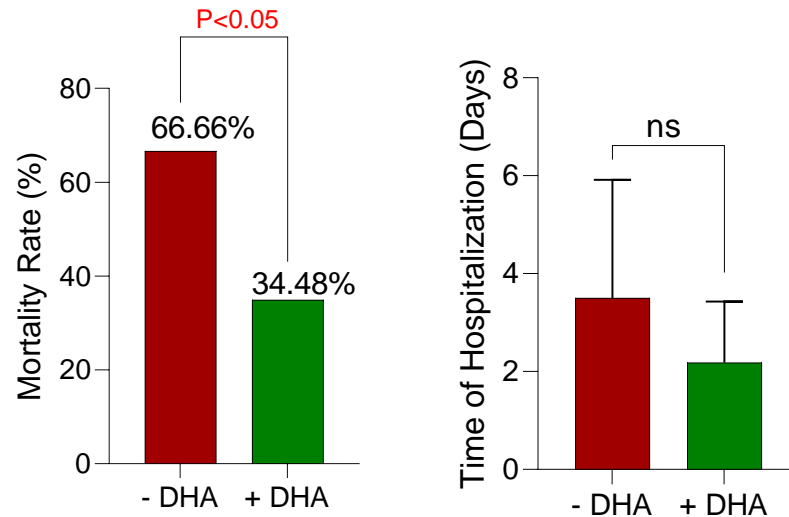


Figure 6. Mortality rate and time of hospitalization of dihydroxyacetone (DHA)-treated patients (+DHA; $n = 58$) in comparison to aluminum phosphide-poisoned patients that did not receive DHA (-DHA; $n = 18$) and were treated based on the routine hospital protocols.

4. Discussion

AIP is widely used in Iran as a pesticide for preserving stored grain, especially rice, from weevil damage.¹ A significant number of accidental or intentional (suicidal attempts) cases of AIP poisoning are recorded annually, and its toxicity is associated with a high mortality rate.^{2,37,38} Unfortunately, there is no specific therapeutic intervention for AIP poisoning, and treatments are primarily supportive care. In the current study, we assessed the antidotal effect of a novel formulation of DHA for intravenous administration in AIP-intoxicated patients. The results indicate prominent antidotal effects of DHA against AIP poisoning as it decreased the mortality rate and normalized biochemical alterations in patients.

Our previous studies on the antidotal effects of DHA revealed that this saccharide could effectively prevent toxicity induced by lethal doses of the mitochondrial toxin cyanide in mice and rabbits *in vivo*, primarily by reversibly binding to CN ion.²⁹⁻³¹ We also previously showed that DHA could antagonize the toxicity of phosphine in cell culture³⁴ and *in vivo* in mice,^{32,33} also by reversible binding to PH_3 . DHA is produced in the form of phosphate in the glycolysis pathway and plays a role in the synthesis of ATP in the cell. Since the primary mechanism of phosphine toxicity is mediated through the inhibition of ATP production in the cell, the entry of DHA into the glycolysis pathway also can prevent the energy (ATP) crisis in cells and inhibit cell death. This is critical for preventing phosphine-induced organ damage, especially in high energy-demanding organs such as the heart and brain. In a recent preclinical animal study, we found that DHA could significantly decrease the mortality rate in phosphine-treated mice.³³ It also significantly restored the cytochrome c oxidase enzyme activity as the primary target for phosphine toxicity in various tissues of phosphine-exposed animals,³³ possibly by reversibly binding to PH_3 and partially restoring cytochrome c oxidase activity.³³ Therefore, the direct effect of DHA on mitochondrial function and energy metabolism plays a central role in its protective properties against AIP toxicity. On the other hand, as mentioned, DHA could also ease ATP production through the glycolysis process in a mitochondria-independent manner.³¹ This unique characteristic of DHA could save the functionality of vital organs such as the brain and heart until appropriate ATP production is restored upon increased cytochrome c oxidase activity.

An interesting finding in the current study was related to some biomarkers, such as acidosis and PaO_2 in AIP-poisoned cases (Fig 4 ND 5). Our data indicated that significant acidosis and decreased PaO_2 are severe clinical manifestations of AIP toxicity associated

with a poor prognosis (Figs 4, 5). We found that all of the poisoned patients who died had a $\text{pH} \leq 7.23$ and a $\text{PaO}_2 \leq 44$ (Fig 5). Based on this data, it could be better to start DHA therapy as soon as possible before pH or PaO_2 levels fall below the above-mentioned values. This simple point might significantly increase the survival rate of AIP-intoxicated patients.

On the other hand, it was found that DHA significantly improved severe acidosis and PaO_2 in AIP-poisoned patients (Fig 4). Based on these data, the effects of DHA on these critical factors could play a vital role in its antidotal mechanisms in AIP toxicity. Unfortunately, although treatment protocols including gastric decontamination (*e.g.*, castor oil), correcting blood acidosis by bicarbonate, administration of drugs for the management of patient agitation, and antihypertensive drugs are routinely followed (Fig 2), still the mortality rate of AIP is very high (up to 80%), depending on factors such as the quality of supportive care, the dose of ingested AIP, and the time of hospitalization.^{39,40} Therefore, there is a need for an effective and rapidly acting agent. This novel DHA i.v. formulation, in addition to its significant antidotal effect, has an accelerated action time, which is its great strength. Also, the administration of oral oils in the cases of AIP poisoning only can partially inhibit the absorption of PH_3 created in the GI tract but cannot affect the already absorbed PH_3 . Administration of i.v. DHA can bind the PH_3 circulating in the blood and present in the cell, as DHA can readily enter the cell.

Recently, a case report of DHA administration in AIP poisoning has been described, in which DHA was orally administered to two cases of AIP-poisoned patients.⁴¹ It should be mentioned that oral administration of DHA in water could increase the risk of PH_3 release from ingested AIP, and it may worsen the patient's condition. As mentioned, AIP poisoning is an emergency state that needs restriction and rapid intervention. Moreover, systemic administration (i.v.) of DHA could counteract the effects of already-absorbed PH_3 in AIP-poisoned patients.

5. Conclusion

Decreasing the mortality rate of AIP-poisoned patients is the tremendous clinical achievement of the current study. We found that parenteral DHA administration tremendously decreased DHA-poisoned patients' mortality rate by about 65%. Interpreting the results of the current study and reaching conclusions are matters of assessing the integrity of the trial's design and the validity of the findings in a more controlled environment as well as on more patients. Finally, this novelty-designed formulation could ultimately find its application on a large scale.

Author Contributions: HN comprehended and designed this study. VA was involved in DHA formulation. RH performed data visualization, manuscript draft preparation, and statistical analysis. AJ was involved in DHA administration to poisoned patients and data collection. MR was involved in data collection and interpretation. All authors were involved in the initial drafting and editing of the manuscript and approved the final version before submission. The corresponding author is the guarantor and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Institutional Review Board Statement: The study was approved by an institutional review board and ethics committee at investigational sites at Shiraz University of Medical Sciences and conducted under the supervision of the Iranian Registry for Clinical Trials (IRCT; Trial registration: IR.SUMS.REC.1394.102), Ministry of Health, and Medical Education guidelines. After a complete description of the study to the patients or their families, written informed consent was obtained.

Data Availability Statement: Deidentified raw data are available upon reasonable request.

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Conflicts of Interest: The authors declare no conflicts of interest.

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