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Atropine Alone vs. Atropine Plus Pralidoxime for Organophosphorus Poisoning: A Randomized Controlled Trial

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Abstract

Organophosphate (OP) poisoning accounts for approximately 300,000 annual global deaths. Despite WHO recommendations, pralidoxime's efficacy alongside atropine for OP poisoning treatment remains uncertain. This study aimed to evaluate whether the addition of pralidoxime to atropine and supportive care provides clinical benefits. A double-blind, randomized, placebo-controlled trial was conducted at Loghman Hakim Hospital in Tehran, Iran, between April 2022 and March 2023. Patients with OP poisoning were randomly allocated to either an intervention group (pralidoxime plus atropine) or a control group (atropine alone). The primary outcome was patient recovery. Secondary outcomes included duration of hospitalization and alteration in paraclinical parameters such as VBG, serum cholinesterase, sodium, potassium, blood glucose, etc., within the initial four hours post-treatment. Sixty participants were included, with 30 patients in each group. The odds of recovery were significantly higher in the control group compared to the intervention group (OR: 4 [95%CI: 1.3-12.6], p = 0.018). However, this difference became nonsignificant after adjusting for baseline discrepancies (adjusted OR: 6.5 [95% CI: 0.96-43.96], p = 0.054). Hospitalization duration was significantly shorter in the control group (6.23 vs 13.31; mean difference: 7.08 [95% CI: 2.17-11.98], p = 0.006). There was no significant between-group difference regarding alteration in paraclinical parameters during the first four hours post-treatment.

The addition of pralidoxime to atropine did not improve survival or reduce hospitalization in OP poisoning. The reasons for this lack of efficacy remain unclear. Further multi-center randomized controlled trials with larger sample sizes are needed to investigate alternative dosing regimens or other oximes.

Keywords: Organophosphates; Pralidoxime compounds; Atropine; Poisoning; Randomized controlled trial.

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1. Introduction

Organophosphates (OPs) are widely used in agriculture for pest control. In developing countries such as India and Sri Lanka, commonly used OP chemicals include methyl parathion, malathion, fenthion, chlorpyrifos, quinalphos, and diazinon [1]. Approximately three million cases of OP poisoning are reported annually, resulting in nearly 300,000 deaths worldwide [2, 3]. This burden disproportionately affects low-resource countries [4].

OP compounds inhibit the acetylcholinesterase (AChE) enzyme by chemically altering its structure, leading to overstimulation of nicotinic and muscarinic receptors and excessive cholinergic activity. Muscarinic receptor overstimulation results in excessive secretions, hyperactivity of the gastrointestinal and urinary tracts, nausea, vomiting, diarrhea, abdominal cramps, loss of bowel and bladder control, and convulsions. Nicotinic receptor overstimulation causes hypertension, tachycardia, muscle cramps, fasciculations, weakness, and paralysis. Death typically occurs due to respiratory failure. Intermediate syndrome, a distinct clinical condition, develops 24 to 96 hours after OP ingestion, following the initial cholinergic crisis but preceding the onset of delayed polyneuropathy [5]. This syndrome is characterized by significant weakness in the neck flexor muscles, respiratory muscles, and proximal limb muscles. While the exact pathophysiology of intermediate syndrome remains incompletely understood, it is thought to result from persistent AChE inhibition, leading to failure of neuromuscular transmission, muscle necrosis, and receptor damage caused by oxidative free radicals [6].

Pralidoxime (2-PAM) is the most commonly used oxime worldwide, available in four salt forms: chloride (2-PAM Cl), methiodide, methyl sulfate, and mesylate (P2S). It is often co-administered with atropine, though its efficacy depends on timely administration before irreversible AChE deterioration occurs [7]. Side effects of 2-PAM include dizziness, drowsiness, blurred or double vision, difficulty concentrating, nausea, headache, tachycardia, hyperventilation, hypertension, and temporary neuromuscular weakness. Laboratory studies consistently show that oximes can effectively restore the activity of human AChE inhibited by OPs [8]. Specific oxime concentrations have been shown to reactivate AChE across various tissues, including blood, muscle, and brain. For pralidoxime, effective reactivation requires significantly higher concentrations (~100 μM), which vary depending on the specific OP involved. Case reports and series indicate that pralidoxime can reactivate OP-inhibited red blood cell AChE [9-11]. Oximes work by restoring the activity of AChE that has bound to OP molecules. They are particularly effective in improving skeletal muscle strength and alleviating diaphragmatic weakness, areas where atropine is less effective [2]. However, the role of pralidoxime in the management of OP poisoning remains controversial. Systematic reviews and meta-analyses have consistently found no significant improvement in clinical outcomes with the use of pralidoxime [12, 13]. This study aimed to determine whether adding pralidoxime chloride to atropine and supportive care offers any clinical benefit in patients with OP poisoning.

2. Materials and Methods

This randomized controlled trial (RCT) was conducted at the clinical toxicology unit of the Loghman Hakim Hospital in Tehran, Iran, between April 2022 and March 2023.

2.1. Study Design and Patient Selection

The study included patients admitted to adult wards with organophosphorus (OP) insecticide poisoning, whether intentional or accidental, who required atropine treatment based on the protocol developed by Eddleston et al. [14]. Exclusion criteria included the following: patients under 18 years old, pregnant individuals, those who had already received pralidoxime at a transferring hospital, cases of mild or asymptomatic poisoning not requiring atropine, and patients with severe preexisting medical conditions. The type of OP insecticide was determined based on the patient's history and clinical presentation. Study physicians assessed patients within 30 minutes of admission and initiated treatment according to the prescribed protocol.

2.2. Sample Size

Sixty eligible patients were enrolled and divided into two groups, each containing 30 patients. The sample size was

calculated using the ClinCalc.com sample size calculator. The following parameters were used for the estimation: a minimum power of analysis of 80%, a maximum Type I error rate (α) of 0.05, an anticipated incidence of 70% in the control group and 30% in the intervention group, and an enrollment ratio of 1:1. The calculated sample size was 23 subjects per group; however, 30 subjects were included in each group. The sample size was determined using the following formula:

$$n = \frac{(Z_{1-\frac{\alpha}{2}} * \sqrt{2\bar{p}(1-\bar{p})} + Z_{1-\beta} * \sqrt{p_1(1-p_1) + p_2(1-p_2)})^2}{(p_1 - p_2)^2}$$

Where:

$Z_{1-\frac{\alpha}{2}}$ is Z-score for desired alpha (i.e., 1.96 for α=0.05, two-tailed)

$Z_{1-\beta}$ is the Z-score for desired power (i.e., 0.84 for 80% power)

p_1 and p_2 are anticipated incidences in two groups (i.e., 0.7 for the control group and 0.3 for the intervention group)

$\bar{p}$ is the mean of p_1 and p_2 (i.e., 0.5)

2.3. Randomization and blinding

The randomization process was conducted using computer-generated random sequences created by an individual not involved in the study implementation or data analysis to ensure the impartial allocation of participants. The study employed a block randomization method, where each block consisted of 10 participants, with five assigned to the treatment group (atropine plus pralidoxime) and the remaining five to the control group (atropine alone). This process was repeated until the required sample size was reached. To ensure concealment, the individual recruiting the patient contacts a central methods center by phone after the patient has been enrolled. The blinding of the study was maintained throughout, meaning that neither the participants nor the outcome assessor knew the group assignments. This ensured a double-blind design, where the patient, the treating staff, and the outcome assessor remained blinded to the allocation, preventing any potential bias or influence on the study outcomes.

2.4. Treatment Protocol

Patients with organophosphorus insecticide poisoning, whether self-inflicted or accidental, were managed using one of two treatment regimens: (1) atropine combined with pralidoxime, or (2) atropine alone. Each atropine ampoule contained 0.5 mg. If cholinergic symptoms, such as rales in the lungs, were present, two ampoules (1mg) were administered intravenously. After waiting 3 to 5 minutes, if the symptoms, including the patient's respiratory status and clinical signs, did not improve, a double dose of 2 mg (equivalent to 4 ampules of 0.5 mg atropine) was administered. After another 3 to 5 minutes, if the symptoms persisted, an additional 4 mg (equivalent to 8 ampoules) was administered. This doubling dose regimen continued until the patient's symptoms, blood oxygen levels, and respiratory status improved, and the rales in the lungs were resolved. This initial loading dose was followed by a maintenance dose, which was set at 20% of the initial dose. Pralidoxime therapy was initiated at a dose of 30 mg/kg. For a patient weighing 70 kg, a dose of 2 g was administered intravenously over 30 minutes, followed by an infusion of 500 mg/hour. Pralidoxime administration was continued until atropine was no longer required for 24 hours.

2.5. Data collection and outcomes

A customized checklist was used to collect data on demographic variables and vital signs at arrival. Additionally, laboratory assessments, including a complete blood count (CBC) with differential, coagulation profile, biochemical markers, and acetylcholinesterase enzyme levels, were evaluated hourly during the first four hours post-treatment. Other variables included the total dose and duration of each treatment, as well as overall hospitalization and outcome. One instructed researcher, who was unaware of the allocation, evaluated the patients and gathered the data.
The primary outcome of the study was the recovery rate, defined as the resolution of cholinergic symptoms caused by organophosphorus poisoning. Recovery included improvements in blood oxygen levels due to the disappearance of rales in the lungs, as well as gradual improvements in cholinesterase enzyme levels. Secondary outcomes included duration of hospitalization and alteration in paraclinical parameters such as VBG, serum cholinesterase, sodium, potassium, blood glucose, etc., within the initial four hours post-treatment.

2.6. Statistical analysis

Data were analyzed using SPSS version 27.0 (IBM, Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation (SD), and comparisons between the atropine-only group and the atropine plus pralidoxime group were made using the independent t-test. Categorical variables were presented as numbers (percent) and evaluated using Pearson's chi-squared test or Fisher's exact test, as appropriate.

To determine the effect of treatment on the main outcome (recovery/death), binary logistic regression was performed. Initially, an unadjusted (crude) odds ratio (OR) was calculated to quantify the association between treatment assignment and the outcome. Recognizing that certain baseline variables exhibited statistically significant discrepancies between the two treatment groups (as identified by independent t-tests and chi-square tests), we subsequently performed an adjusted binary logistic regression. In this model, the outcome was regressed on the treatment group, adjusting for these imbalanced baseline characteristics to account for potential confounding effects. For both the unadjusted and adjusted models, the odds ratio (OR) with its corresponding 95% confidence interval (CI) was reported. A p-value of less than 0.05 was considered statistically significant.

To evaluate the alteration of parameters measured at four distinct time points across the two treatment groups, a general linear model (GLM) for repeated measures was used. The main effect of time (within-subjects effect), the main effect of group (between-subjects effect), and their interaction (Time × Group) were measured to determine if the change in parameters over time differed between the two groups. Mauchly's test of sphericity was conducted, and if the assumption of sphericity was violated ($p<0.05$), the degrees of freedom were adjusted using the Greenhouse-Geisser correction. The F-statistic, its corresponding degrees of freedom, and the p-value were reported. Additionally, partial eta-squared (η^2_p) was reported as a measure of effect size. A p-value of less than 0.05 was considered statistically significant.

2.7. Ethical consideration

This study has been approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences with code IR.SBMU.RETECH.REC.1401.772.

3. Results and Discussion

3.1. Baseline characteristics

The study enrolled 60 participants, divided into two groups: 30 patients received only atropine, while 30 patients received pralidoxime in addition to atropine. There was no attrition and, therefore, an intention-to-treat analysis was not required (**Figure 1**).

Baseline characteristics of patients in each group are demonstrated in **Table 1**. The mean age of the atropine-only group was 40.4 ± 20 years, whereas the pralidoxime plus atropine group had a mean age of 55.57 ± 23.7 years ($p = 0.06$). No significant difference in sex distribution and other baseline characteristics was observed between the two groups except for the reason of poisoning (intentional/accidental), rate of co-ingestion, level of serum cholinesterase, and systolic and diastolic blood pressure. In the control group, one patient presented with a neurological disorder, another with hepatic disease, and one patient had co-occurring ischemic heart disease and a cerebrovascular accident. In the intervention group, two patients had a history of hypertension and heart disease, two patients had diabetes, and one patient experienced both ischemic heart disease and a cerebrovascular accident.

Regarding nicotinic symptoms, muscular weakness was observed in only two patients in the intervention group. Similarly, only two patients in the intervention group exhibited an altered plantar reflex. No patients in either group experienced seizures, sialorrhea, or shortness of breath. Furthermore, no significant differences were observed between the two groups in terms of ECG findings. The duration of atropine infusion (5.1 ± 3.2 vs 8.1 ± 5.2; $p = 0.34$), duration of hospitalization (6.23 ± 4.73 vs 13.31 ± 11.52; $p = 0.006$), and the percentage of mortality (20% vs 50%; $p = 0.015$) were significantly higher in the intervention group compared to the control group (**Table 1**).

3.2. Effects of treatment on outcome

Binary logistic regression was performed to assess the association between treatment group and the outcome of death or recovery, both unadjusted and adjusted for baseline imbalances. Initially, a crude (unadjusted) analysis showed that the intervention (pralidoxime plus atropine vs. atropine alone) was significantly associated

with the outcome, with an odds ratio (OR) of 4.00 [95% CI: 1.3–12.6], p = 0.018. This suggests that patients receiving the intervention (atropine plus pralidoxime) had four times lower odds of recovery (or higher odds of death) compared to those receiving atropine alone, without accounting for other factors. However, after adjusting for baseline discrepancies in reason of poisoning, co-ingestion, systolic blood pressure, and diastolic blood pressure, the association between the intervention and the outcome became borderline statistically significant, with an adjusted odds ratio (AOR) of 6.50 [95% CI: 0.96–43.96], p = 0.054. This indicates that while the point estimate for the adjusted effect of the intervention is larger, the wide confidence interval, which includes 1, suggests that the effect is not statistically significant at the conventional p < 0.05 level after accounting for these other variables (**Table 2**). The higher adjusted odds ratio, along with a borderline p-value, suggests a potentially meaningful association that did not reach conventional levels of statistical significance, warranting cautious interpretation and further investigation.

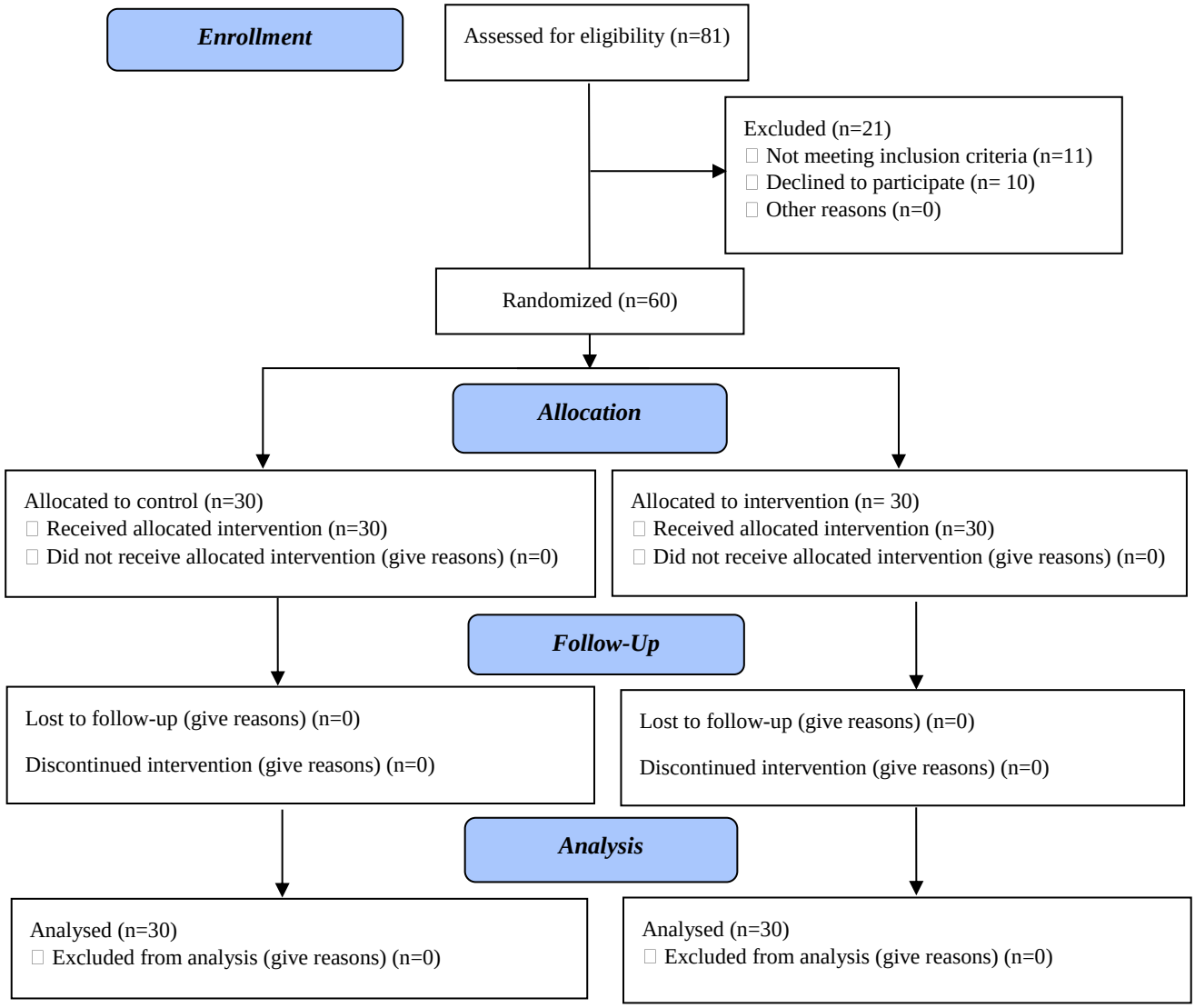

Figure 1. The consort flow chart of participants.

Table 1. Baseline demographic and paraclinical characteristics of patients

Variables		Control group (n = 30)	Intervention group (n = 30)	P-value
Age, mean (SD)		40.40 (20)	55.57 (23.7)	0.06
Sex, n (%)	Male	15 (50)	13 (43.3)	0.6
	Female	15 (50)	17 (56.7)	
Reason of poisoning, n (%)	Intentional	26 (86.7)	18 (60)	**0.02***
	Accidental	4 (13.3)	12 (40)	
Amount of consumption (ml), mean (SD)		239.33 (193.7)	174 (133.1)	0.27
Time elapse from consumption to admission, mean (SD)		3.1 (2)	3.3 (2.3)	0.94
Co-ingestion, n (%)	Yes	10 (33.3)	2 (6.7)	**0.01***
	No	20 (66.7)	28 (93.3)	
Underlying disease, n (%)	Yes	3 (10)	5 (16.7)	0.3
	No	27 (90)	25 (83.3)	
GCS, mean (SD)		13.69 (2.5)	13.15 (3)	0.13
Diarrhea, n (%)	Yes	12 (40))	18 (60)	0.12
	No	18 (60)	12 (40)	
Sweating, n (%)	Yes	1 (3.3)	4 (13.3)	0.16
	No	29 (96.7)	26 (86.7)	
Rhinorrhea, n (%)	Yes	4 (13.3)	7 (23.3)	0.32
	No	26 (86.7)	23 (76.7)	
Urinary Incontinence, n (%)	Yes	4 (13.3)	7 (23.3)	0.32
	No	26 (86.7)	23 (76.7)	
Pulmonary rales, n (%)	Yes	5 (16.7)	5 (16.7)	1
	No	25 (83.3)	25 (83.3)	
Neck flexion, n (%)	Yes	2 (6.7)	3 (10)	0.3
	No	28 (93.3)	27 (90)	
Aspiration pneumonia, n (%)	Yes	1 (3.3)	1 (3.3)	1
	No	29 (96.7)	29 (96.7)	
Respiratory rate (/min), mean (SD)		16.9 (3.3)	18 (4.6)	0.14
Pulse rate (/min), mean (SD)		93.3 (16.7)	88.6 (20)	0.13
Temperature (°C), mean (SD)		36.9 (0.3)	36.8 (0.4)	0.52
Systolic Blood pressure (mmHg), mean (SD)		123.1 (18.3)	135.8 (25.4)	**0.016***
Diastolic Blood pressure (mmHg), mean (SD)		78.2 (11.2)	76.6 (15)	**0.027***
Level of cholinesterase (U/L), mean (SD)		1521.1 (3180.1)	420.1 (755.9)	**<0.001***
PH value, mean (SD)		7.3 (0.1)	7.3 (0.07)	0.78
PCO2 (mmHg), mean (SD)		40.5 (8.1)	41.9 (8)	0.67
PO2 (mmHg), mean (SD)		49 (25.6)	56.7 (30.8)	0.17
HCO3, mean (SD)		22.4 (2.8)	21.1 (2.2)	0.12
Sodium (mEq/L), mean (SD)		139.5 (2.8)	139 (3.1)	0.67
Potassium (mEq/L), mean (SD)		3.6 (0.4)	3.6 (0.3)	0.81
Blood Sugar (mg/dL), mean (SD)		169.2 (58.2)	211.4 (61.9)	0.95
Creatinine (mg/dL), mean (SD)		1.2 (1.2)	1 (0.5)	0.13
Blood Urea Nitrogen (mg/dL), mean (SD)		40.4 (34.3)	43 (34.1)	0.95
White Blood Cell count (10^9/L), mean (SD)		14.7 (7.4)	17.4 (8.2)	0.42
Hemoglobin (g/dL), mean (SD)		14 (1.6)	14.5 (1.5)	0.37
Hematocrit (%), mean (SD)		42.1 (4.1)	43.2 (4.4)	0.96
Platelet (10^9/L), mean (SD)		278 (73.5)	261 (69.2)	0.76
Aspartate Transaminase (IU/L), mean (SD)		32.3 (9.3)	32.7 (11.5)	0.16
Alanine Transaminase (IU/L), mean (SD)		21.8 (9.4)	22.4 (12.5)	0.23
Alkaline phosphatase (IU/L), mean (SD)		370 (288.6)	306.3 (237)	0.09
Lactate Dehydrogenase (IU/L), mean (SD)		515.1 (185.2)	562.8 (192.9)	0.56
Creatine Phosphokinase (IU/L), mean (SD)		168.1 (131)	174.2 (157.8)	0.18
Prothrombin Time (sec), mean (SD)		12.5 (0.6)	12.6 (1)	0.55
Partial Thromboplastin Time (sec), mean (SD)		34.6 (11.8)	34.3 (12.6)	0.91
International Normalized Ratio, mean (SD)		1 (0.08)	1.1 (0.09)	0.86
Atropine blouse (mg), mean (SD)		7.5 (13)	7 (12)	0.73
Total amount of atropine (gr), mean (SD)		9.6 (10.6)	16.1 (20.4)	0.1
Duration of atropine infusion (day), mean (SD)		5.1 (3.2)	8.1 (5.2)	**0.034***
Pralidoxime blouse (mg), mead (SD)		-	1 (0.6)	-
Total amount of pralidoxime (mg), mean (SD)		-	570 (186.2)	-
Duration of hospitalization (day), mean (SD)		6.23 (4.73)	13.31 (11.52)	**0.006***
Outcome, n (%)	Discharge	24 (80)	15 (50)	**0.015***
	Death	6 (20)	15 (50)	

Table 2. Crude and adjusted odds ratios for factors associated with outcome (Death or Recovery)

Variables	Crude OR (95% CI)	p-Value	Adjusted OR (95% CI)	p-Value
Intervention (pralidoxime plus atropine/atropine alone)	4 (1.3-12.6)	0.018	6.5 (0.96-43.96)	0.054
Reason of poisoning (intentional/accidental)	3.43 (1.04-11.27)	0.042	1.96 (0.39-9.82)	0.412
Co-ingestion (Yes/No)	2.2 (0.61-8)	0.23	4.81 (0.47-49.65)	0.187
Systolic Blood pressure (mmHg)	1.07 (1.03-1.1)	<0.001	1.04 (0.99-1.09)	0.109
Diastolic Blood pressure (mmHg)	1.09 (1.04-1.15)	0.001	1.04 (0.96-1.13)	0.305
Level of cholinesterase (U/L)	0.99 (0.99-1)	0.285	1 (0.99-1)	0.497

Additional individual adjustments for specific baseline characteristics provided further insight into the treatment's efficacy on the outcome. When adjusting solely for age, the odds ratio for the intervention remained nonsignificant (AOR = 1.70 [95% CI: 0.36–8.05], p=0.505). Interestingly, adjusting only for diastolic blood pressure yielded a statistically significant increase in the odds ratio for the intervention (AOR = 7.49 [95% CI: 1.70–32.96], p=0.008). Similarly, adjusting solely for co-ingestion also resulted in a statistically significant and increased odds ratio for the intervention (AOR = 9.38 [95% CI: 1.89–46.47], p = 0.006) (data were not shown in **Table 2**).

Reason of poisoning was significantly associated with the outcome in the crude analysis (OR = 3.43 [95% CI: 1.04–11.27], p = 0.042), but this association was no longer significant in the adjusted model (AOR = 1.96 [95% CI: 0.39–9.82], p = 0.412). Co-ingestion was not significantly associated with the outcome in either the crude (OR = 2.20 [95% CI: 0.61–8.0], p = 0.23) or adjusted models (AOR = 4.81 [95% CI: 0.47–49.65], p = 0.187). Systolic blood pressure and diastolic blood pressure showed significant associations with the outcome in the crude models (SBP: OR = 1.07 [95% CI: 1.03–1.1], p < 0.001; DBP: OR = 1.09 [95% CI: 1.04–1.15], p = 0.001). However, these associations were no longer statistically significant in the adjusted model (SBP: AOR = 1.04 [95% CI: 0.99–1.09], p = 0.109; DBP: AOR = 1.04 [95% CI: 0.96–1.13], p = 0.305). Level of cholinesterase was not significantly associated with the outcome in either the crude (OR = 0.99 [95% CI: 0.99–1.0], p = 0.285) or adjusted models (AOR = 1.0 [95% CI: 0.99–1.00], p = 0.497). The full results of the binary logistic regression analyses are presented in **Table 2**.

3.3. Paraclinical Parameters Over Time

We used a GLM for repeated measures to evaluate the alteration of some paraclinical parameters between the two treatment groups (Control and Intervention) across four time points (hour 1, 2, 3, and 4 post-treatment). **Table 3** presents the mean values (SD) for each parameter at each time point, along with the results of the within-subjects (Time), between-subjects (Treatment groups), and Time/Groups interaction effects.

Across both groups, significant changes over time (within-subjects effects) were observed for all measured paraclinical parameters except for creatinine and BUN. However, no statistically significant main effects of treatment groups were found for any of the measured paraclinical parameters (between-subjects effects), indicating that, on average across all time points, there were no overall significant differences between the Control and Intervention groups for the measured parameters across four time points. Furthermore, there were no statistically significant Time/Group interactions for any of the measured paraclinical parameters (**Table 3**). The lack of significant Time/Group interactions indicates that the pattern of change over the four hours for each parameter did not significantly differ between the Control and Intervention groups. Despite the significant changes over time observed for many parameters, these changes occurred similarly in both groups.

Table 3. Paraclinical parameters over four hours post-treatment and results of repeated measures GLM analysis

Variables	Groups	hour 1 post-treatment, mean (SD)	hour 2 post-treatment, mean (SD)	hour 3 post-treatment, mean (SD)	hour 4 post-treatment, mean (SD)	Within-subjects effects (Day), F (df1, df2), p, η^2_p	Between-subjects effects (group), F (df1, df2), p, η^2_p	Time*group interaction, F (df1, df2), p, η^2_p
Level of cholinesterase (U/L)	Control	453 (371.9)	1208 (746.7)	566 (659)	1207.5 (587.6)	37.4 (1, 3), 0.009, 0.926	0.086 (1, 3), 0.789, 0.028	0.086 (1, 3), 0.789, 0.028
	Intervention	365.3 (303.7)	1032 (609.7)	410.7 (538.1)	1069 (479.7)			
PH value	Control	7.3 (0.1)	7.37 (0.05)	7.38 (0.04)	7.34 (0.1)	9.5 (2, 71.2), <0.001, 0.213	2.1 (1, 35), 0.16, 0.06	1.4 (2, 71.2), 0.24, 0.04
	Intervention	7.3 (0.07)	7.37 (0.05)	7.38 (0.03)	7.29 (0.1)			
PCO2 (mmHg)	Control	43.14 (8.3)	33.8 (7.9)	38.59 (4.2)	44.05 (6.9)	20.6 (2.2, 76.8), <0.001, 0.37	1.12 (1, 35), 0.3, 0.031	1.4 (2.2, 76.8), 0.25, 0.038
	Intervention	43.12 (9)	32.9 (5.8)	39.21 (6.8)	49.89 (10.1)			
PO2 (mmHg)	Control	58.8 (31)	85.2 (44.5)	53.7 (22.4)	46.9 (14.5)	7.12 (2, 71.2), 0.001, 0.17	0.341 (1, 35), 0.563, 0.01	0.172 (2, 71.2), 0.846, 0.005
	Intervention	64.2 (32.8)	81 (46)	59.3 (28.9)	50.4 (13.16)			
HCO3	Control	21.29 (1.8)	21.2 (4.9)	23.4 (2.5)	23.3 (5.3)	7.46 (1.7, 61.2), 0.002, 0.176	0.04 (1, 35), 0.843, 0.001	0.476 (1.7, 61.2), 0.6, 0.013
	Intervention	20.41 (1.3)	20.3 (3.8)	23.9 (1.9)	23.9 (6.4)			
Sodium (mEq/L)	Control	139.8 (3.3)	139.3 (5.2)	136 (3.9)	132.23 (4.3)	51.9 (2.4, 87.4), <0.001, 0.584	0.278 (1, 37), 0.6, 0.007	2.6 (2.4, 87.4), 0.067, 0.067
	Intervention	139.2 (3.2)	139.2 (4.7)	138.9 (3.4)	132.18 (3.6)			
Potassium (mEq/L)	Control	3.6 (0.4)	3.8 (0.5)	3.8 (0.5)	4.1 (0.6)	15.3 (1.5, 57.6), <0.001, 0.3	0.21 (1, 37), 0.64, 0.006	0.36 (1.5, 57.6), 0.647, 0.01
	Intervention	3.5 (0.3)	3.8 (0.6)	3.7 (0.3)	4.1 (0.7)			
Blood Sugar (mg/dL)	Control	198 (49.5)	112.7 (28.8)	97.5 (9.9)	82.5 (24.9)	96.7 (1.6, 69.9), <0.001, 0.69	2.9 (1, 43), 0.094, 0.064	0.35 (1.6, 69.9), 0.66, 0.008
	Intervention	210.6 (56.5)	114.1 (28.2)	112.9 (34)	95.2 (34.2)			
Creatinine (mg/dL)	Control	1.4 (1.5)	1.2 (0.7)	1.3 (1.1)	1.1 (1)	0.27 (2, 81.8), 0.76, 0.007	0.57*4 (1, 41), 0.45, 0.014	0.97 (2, 81.8), 0.38, 0.023
	Intervention	1 (0.6)	1.3 (0.7)	1 (0.6)	1.1 (0.7)			
Blood Urea Nitrogen (mg/dL)	Control	46.4 (42.3)	51.5 (36.1)	49.4 (42.8)	41.3 (22.8)	1.43 (2.3, 94.8), 0.244, 0.034	0.034 (1, 41), 0.85, 0.001	1.8 (2.3, 94.8), 0.17, 0.042
	Intervention	43.8 (38)	56.8 (43.4)	40.4 (27.4)	54.5 (36.9)			
White Blood Cell count (10^9/L)	Control	17.1 (8.1)	16.6 (7.3)	7.9 (3.5)	14 (4.5)	19.8 (1.5, 55.6), <0.001, 0.34	0.06 (1, 38), 0.8, 0.001	0.39 (1.5, 55,6), 0.6, 0.01
	Intervention	18.1 (9.7)	17.3 (7.6)	9 (3)	12.5 (5.5)			
Hemoglobin (g/dL)	Control	14.5 (1.7)	13.4 (2.1)	11.9 (1.4)	10.1 (2)	67.1 (2.1, 62), <0.001, 0.7	0.26 (1, 30), 0.6, 0.01	0.5 (2.1, 62), o.6, 0.016
	Intervention	14.6 (1.9)	14 (2.3)	12 (1.5)	11.3 (2.2)			
Hematocrit (%)	Control	43 (4.7)	40.16 (6.9)	35.7 (4.7)	33.2 (7.7)	22.9 (1.8, 58.2), <0.001, 0.42	0.017 (1, 32), 0.9, 0.001	0.3 (1.8, 58.2), 0.7, 0.009
	Intervention	43.6 (5.1)	38.6 (11.7)	36.2 (4.1)	32.6 (10.1)			
Platelet (10^9/L)	Control	295.9 (59.4)	264.3 (55.8)	214.2 (62.1)	225.6 (133.6)	10 (1.3, 40.4), 0.002, 0.24	0.003 (1. 32), 0.9, <0.001	0.1 (1.3, 40.4), 0.8, 0.003
	Intervention	289 (73.1)	263.4 (64.5)	223.7 (77.9)	228.9 (127)			

3.4. Discussion

This study aimed to evaluate the efficacy and safety of pralidoxime in combination with atropine for the treatment of symptomatic organophosphate (OP) pesticide poisoning. Recovery was defined as the resolution of cholinergic symptoms caused by organophosphorus poisoning, including improvements in blood oxygen levels and gradual restoration of cholinesterase enzyme activity. This definition aligns with other studies in the literature, which characterize recovery by both clinical and biochemical markers.

Surprisingly, our findings revealed that pralidoxime pulse atropine not only offered no measurable benefit compared to atropine alone but also resulted in poorer outcomes. Patients receiving pralidoxime plus atropine in our study experienced longer hospital stays and higher mortality compared to patients receiving atropine alone. However, these observed differences became nonsignificant after adjusting for baseline variables that significantly differed between the groups. This suggests that the initial discrepancies in these baseline variables may have had a confounding effect, resulting in a falsely significant difference in outcomes between the two treatment groups. After adjustment, the resultant nonsignificant difference between the two groups raises important questions regarding the clinical utility of pralidoxime, suggesting that the drug may not be as effective as previously believed in treating severe OP poisoning. The contrast between our results and those of prior studies, which have shown potential benefits of pralidoxime, highlights several key issues. One possible explanation for this discrepancy is the timing of treatment administration. In our study, pralidoxime was given after patients had already experienced significant poisoning, potentially diminishing its efficacy. Other studies that reported more favorable outcomes may have initiated pralidoxime therapy at an earlier stage of poisoning or followed different treatment protocols.

Despite promising in vitro and animal studies showing that oximes, such as pralidoxime, can reactivate AChE inhibited by OP compounds, translating these findings into clinical efficacy in humans has proven difficult [15, 16]. Several studies have reported mixed results, and our study adds to the growing body of evidence indicating that pralidoxime may not provide the anticipated clinical benefit in severe cases of OP poisoning. Some studies recommend that oximes should be used routinely in organophosphate poisoning [17]. The one study in volunteers found that pralidoxime increased AChE activity and resolved mild symptoms [9], but its clinical relevance for severe poisoning remains uncertain. Our study highlights the importance of considering the severity of poisoning, as higher toxin burdens may reduce the effectiveness of pralidoxime in severe cases. However, considering the small sample size and single-center study, the recommendation against pralidoxime administration in patients with OP poisoning should be stated more carefully.

RCTs have evaluated pralidoxime for the treatment of organophosphate poisoning, examining various formulations and dosing regimens. The Baramati RCT reported positive results with high-dose pralidoxime iodide, administered within the first 48 hours after a loading dose. This outcome was attributed to higher drug concentrations, earlier treatment initiation, and less severe baseline conditions in patients [18, 19]. An analysis from Sri Lanka found no significant difference in outcomes for patients with organophosphate poisoning treated with atropine alone during periods when pralidoxime was unavailable [1]. This supports the idea that pralidoxime might not provide significant additional benefit in severe cases of poisoning, particularly when timely and adequate atropine therapy is already administered. Several researchers have suggested that the standard pralidoxime dosage may be insufficient to achieve the desired therapeutic effect [20-24]. A study conducted in the UK highlighted significant limitations in pralidoxime treatment, including issues related to timing, dosage, and adverse effects [25].

Additionally, A systematic review and meta-analysis by Kharel H. et al. reported that pralidoxime did not demonstrate a benefit in patients with acute organophosphate (OP) poisoning [26]. This aligns with our findings, where pralidoxime administration failed to produce positive outcomes, possibly due to suboptimal dosing or delayed treatment. The costs and logistical challenges associated with pralidoxime use are considerable, and our findings suggest that it may not be a justifiable addition to atropine in clinical practice, particularly in resource-limited settings.

However, these results should be interpreted with caution due to several limitations. We were unable to determine the specific toxin ingested by patients in this study. This poses a limitation, given that treatment efficacy is recognized to differ based on the different stages of aging and the pharmacodynamics of different opioids. Providing more detailed information about the types of organophosphate (OP) agents could have offered additional context for our findings. We also could not assess the relationship between plasma concentrations of atropine and pralidoxime and clinical outcomes, as these measurements were not performed.

Furthermore, we did not evaluate serum or urine levels of organophosphorus compounds. Finally, we were unable to measure RBC or CNS cholinesterase activity. This is a limitation because pralidoxime may positively affect the activation of RBC or CNS cholinesterase, potentially reducing the likelihood of late neurological sequelae following organophosphate (OP) poisoning. Although all patients had clear histories and clinical signs of acute OP poisoning, there remains the possibility of exposure misclassification, which could have influenced our results.

4. Conclusion

The current evidence regarding mortality and the need for ventilator support is insufficient to justify the routine use of pralidoxime in acute organophosphate poisoning. Although our findings suggest that pralidoxime administration did not offer significant benefit in OP poisoning management, the single-site design and limited sample size of our study necessitate cautious interpretation. Therefore, definitive recommendations against the use of pralidoxime should be made with careful consideration. Treatment should be individualized based on the severity of symptoms, the type and amount of OP chemical ingested, and the time since exposure. Identifying specific patient subgroups that may benefit from pralidoxime and optimizing dosing strategies are essential for improving outcomes. Future multi-center randomized controlled trials with larger sample sizes should stratify patients according to severity, time to treatment, type of OP, RBC AChE activity, and the potential for ex vivo reactivation. Future studies should investigate pralidoxime dosing regimens, pharmacokinetics, and the specific organophosphate compounds involved to determine more effective treatment strategies. Additionally, animal models and genetic studies could provide valuable insights into the pharmacodynamics and individual variations in treatment response.

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Conflict of interest

None.

Data availability

Data is available upon request from the corresponding author.

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Using artificial intelligence chatbots

There was no use of artificial intelligence in the making of this article.

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