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The Association Between QTc-Interval and Blood Glucose with Plasma Acetylcholinesterase in Organophosphate (OP)-Poisoned Patients

Maryam ZaareNahandi [1], Ali Ostadi [2], Mahdi khodayari [3], Amin Azimi [3], Ahad Banagozar Mohammadi [4], Alireza Ghaffari [2], Ali Banagozar Mohammadi [4,*]

[1] Kidney Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[2] Department of Internal Medicine, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[3] Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
[4] Medical Philosophy and History Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

[*] *Corresponding author:* Department of Internal Medicine, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran. Telephone number: +98 (41) 35498260, Fax: +98 (41) 35498406 Email: alibanagozar@gmail.com

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Abstract

Background: Organophosphate (OP) poisoning ranks among the leading causes of poisoning, morbidity, and mortality in developing countries due to its relatively high prevalence and potentially grave outcomes. Consequently, it is crucial to identify an easily accessible and cost-effective marker that can be utilized across healthcare facilities.

Objectives: This study aimed to explore the relationship between the QTc interval and blood glucose levels with serum cholinesterase levels in patients poisoned by organophosphates.

Methods: The sample consisted of all patients admitted with OP poisoning to a Northwest Poisoning Center in Iran during 2016 and 2017. Diagnosis of OP poisoning was confirmed through patient history, physical examination, or the measurement of acetylcholinesterase levels. Data collected were analyzed using SPSS software version 25.

Results: Results: Out of 238 patients, 104 remained after applying exclusion criteria and were included in the study. The mean age of these patients was 30.81 ± 15.04 years. A statistically significant negative correlation was found between average blood glucose and serum cholinesterase levels ($P = 0.046$, Pearson Correlation = -0.196). Furthermore, patients with abnormal QTc intervals exhibited significantly lower serum cholinesterase levels ($P < 0.001$).

Conclusions: The findings indicate a significant association between QTc intervals and blood glucose levels with serum cholinesterase levels. Serum cholinesterase levels decreased with an increase in QTc intervals and blood glucose levels. Specifically, patients with a QTc interval greater than 440 milliseconds or random blood glucose levels above 200 milligrams per deciliter showed significantly lower serum cholinesterase levels.

Keywords: Acetylcholinesterase, Organophosphate (OP), Poisoning, QTc-interval, Blood Glucose

1. Background

Organophosphates (OP) are a category of phosphorus-containing chemical containing phosphorus, widely utilized in various applications, including compounds extensively used in agriculture and household insecticides. They act as insecticides by interfering with the nervous systems of insects, leading to paralysis and death (1). Beyond their industrial, agricultural, and domestic applications, these substances have also been employed as nerve agents in warfare and terrorist acts (2). Organophosphates can be absorbed through ingestion, inhalation, skin contact, mucosal exposure, or intravenous injection, resulting in toxicity. They inhibit the enzyme acetylcholinesterase, leading to an excess of acetylcholine at cholinergic synapses. The severity of poisoning and the accumulation site of acetylcholine dictate whether muscarinic or nicotinic symptoms will manifest (1-3).

A considerable number of OP poisoning incidents are attributed to the easy availability of these compounds. This accessibility implies that these chemicals might not always be managed or stored properly, coupled with unregulated sales, heightening the risk of both intentional and accidental poisonings (3). In developing countries, OP compound poisonings lead to a

significant number of deaths (1). Although recent research has focused on treatment methods, the mortality rate associated with OP poisoning continues to be substantial. Prompt diagnosis, specialized care, and appropriate treatments are crucial for decreasing OP-related deaths (3, 4). In Iran, OP poisoning represents a major public health issue. As reported by Shadnia et al., organophosphates constitute the primary cause of poisoning and pesticide-related fatalities in Tehran, the capital city of Iran. Even with adequate treatment, the mortality rate there can reach up to 30 percent (5). Thus, assessing the severity of OP poisoning and mortality risks is essential for efficient resource allocation and ensuring effective treatment. The severity of OP poisoning is generally assessed by measuring cholinesterase levels and observing clinical signs and symptoms (3-7).

The diagnosis of OP poisoning is typically made through a combination of clinical presentation, physical examination, and laboratory tests, with cholinesterase-level results often providing confirmation. This method enables healthcare professionals to accurately identify cases of OP poisoning, facilitating prognosis and the determination of appropriate treatment. The cholinesterase assay serves as a crucial tool in confirming OP poisoning and guiding treatment by offering objective evidence of exposure to these toxic chemicals (6, 7). Research has linked the type of OP ingested to prognostic factors such as blood glucose level at admission, blood cholinesterase level, QTc interval, the specific type and amount of OP poison consumed, age, IPCS PSS Poison Severity Score (PSS), and GCS, Glasgow Coma Scale (GCS) scores (3, 6-10). Although increases in QTc interval and blood glucose level are considered prognostic factors for OP poisoning, their relationship with acetylcholinesterase levels remains uncertain. Moreover, while the measurement of blood cholinesterase levels is crucial for assessing the severity of poisoning, the availability of this test is not consistent across all locations and times in Iran.

2. Objectives

Given the relatively high incidence of OP poisoning in Iran and its potentially grave outcomes, establishing an easily accessible and cost-effective indicator for use across specialized medical fields and healthcare centers is vital. Such an indicator would help in predicting potential complications, thereby enabling effective patient monitoring and prevention of adverse effects. Therefore, this study aims to explore the relationship between QTc interval and blood glucose levels (as 2 readily available and cost-effective measures) with serum cholinesterase levels in hospitalized patients with OP poisoning at the Northwest Poisoning Center of Iran - Sina Teaching Hospital, Tabriz. The goal is to identify severe cases of OP poisoning using easy and accessible evaluation methods.

3. Methods

In this cross-sectional study, all patients hospitalized with OP poisoning at Sina Hospital - the Northwest Poisoning Center of Iran - during 2016 and 2017 were included as the study sample. The inclusion criteria encompassed patients admitted to the poisoning wards, with an initial diagnosis made by a medical toxicologist based on the symptoms reported by the patient and findings from the physical examination. Additionally, a serum cholinesterase test confirmed the diagnosis in cases where the type of poisoning was uncertain or when confirmation was deemed necessary. Patients who met any of the exclusion criteria were not included in the study. The exclusion criteria were as follows:

(1) Individuals with pre-existing conditions such as diabetes, cardiovascular diseases, respiratory diseases, kidney failure, and liver failure.

(2) Patients who had undergone surgery within one month prior to the poisoning incident.

(3) Individuals who had ingested other drugs or poisons concurrently with the OP poisoning.

(4) Patients who showed adequate response to the coma cocktail (comprising dextrose, naloxone, and thiamine) upon admission due to a decreased level of consciousness.

(5) Patients who had received medical interventions like gastrointestinal decontamination, atropine, pralidoxime, intubation, and ventilation at other centers before being referred to the Sina Poisoning Center.

(6) Patients presenting with electrolyte disorders, including hypo- or hypernatremia, hypo- or hyperkalemia, hypo- or hypercalcemia, and hypo- or hypermagnesemia.

(7) Patients whose medical records and clinical examination did not reveal symptoms indicative of OP poisoning.

(8) Patients who tested positive for other poisons or drugs in urine screenings.

In this study, correlation analyses were conducted among the QTc interval (measured in milliseconds), blood glucose (measured in milligrams per deciliter), and plasma acetylcholinesterase levels exclusively

within a group of patients poisoned by OP, designating the study as a descriptive cross-sectional type.

The sample size was determined using data from a pilot study. The pilot study indicated an average deviation in QTc interval size of 76 ($msec^2$) and a correlation coefficient of 80% among the patients studied. We assumed a maximum estimation error of not more than 20 $msec^2$. With a 95% confidence level (accounting for a 5% type I error and a 20% type II error), a minimum of 58 samples was estimated to be necessary. Considering the opinions and experiences of the study designers about the need to increase the sample size, and after applying the inclusion and exclusion criteria of the study, a total of 104 cases were eventually included in the study.

To gather patient information, researchers reviewed and extracted relevant data from the medical records and files of the selected patients in the Medical Documentation Unit of Sina Hospital. The collected data were analyzed using SPSS software version 25. Descriptive data were presented as frequency, percentage, and quantitative data as mean ± standard deviation for normally distributed data. Statistical tests such as the chi-square, *t*-test, and regression were employed, setting the significance level for decision-making regarding the proposed hypotheses at $P < 0.05$.

For this study, the normal range for serum cholinesterase enzyme levels for both genders was considered to be between 5000 and 12000 units per liter. Additionally, the normal range for the QTc interval, calculated using the Bazett formula, was established as between 360 and 440 milliseconds for both genders. The normal range for random blood glucose levels was set between 70 and 200 milligrams per deciliter.

No diagnostic, therapeutic, or pharmaceutical interventions were conducted on the patients as part of this study. Instead, the only information available in the medical records, such as diagnoses, medical histories, examinations, and laboratory tests, was used for research purposes. These records represent routine paraclinical procedures at the Poisoning Center. Ethical approval for the study was granted by the Regional Ethics Committee, with the first approval received on March 12, 2018, under the code IR.TBZMED.REC.1396.1300 is used to investigate the association between blood glucose levels in these patients. The second approval was obtained on July 23, 2018, under the code IR.TBZMED.REC.1397.378, for researching the association with the QTc interval in these patients.

4. Results

In this study, 238 patients who were poisoned with organophosphorus compounds (125 males and 113 females) were initially considered. After applying the exclusion criteria, 104 patients remained and were included in the study. The mean age of the patients was 30.81 ± 15.04 years, with the youngest being 14 years old and the oldest 87 years old.

Of these patients, 52 (50%) were male, and 52 (50%) were female. In terms of marital status, 31 patients (29.8%) were single, 70 patients (67.3%) were married, and three patients (2.9%) were divorced. Regarding the patients' residence, 33 individuals (31.7%) lived in the city of Tabriz, 9 individuals (8.7%) lived in other cities around Tabriz, and 62 individuals (59.6%) came from rural areas. Concerning educational level, 13 patients (12.5%) were illiterate, 22 patients (21.2%) had elementary education, 28 patients (26.9%) completed middle school, 32 patients (30.8%) completed high school, and nine patients (8.7%) had university education. A total of 81 individuals (77.9%) had intentionally poisoned themselves, while 23 individuals (22.1%) had ingested the poisons unintentionally or accidentally. Among those who intentionally poisoned themselves, 50 individuals (61.0%) were from rural areas, and 31 (39.0%) were from urban areas.

In assessing the QTc interval using the Bazett formula based on ECG records, the mean value was 408.63 ± 76.79 milliseconds, with the minimum value at 200 milliseconds and the maximum at 630 milliseconds (Table 1). Fifty-four individuals (51.9%) had a normal QTc interval, 19 individuals (18.3%) had a shorter QTc interval, and 31 individuals (29.8%) had a longer QTc interval.

Table 1. The Characteristics of Key Factors Affecting the Prognosis of Organophosphate Poisoning in Both Men and Women

Variables	Mean (SD)	Median	Min	Max	P
QTc (msec)					0.720
Total	408.63 (76.79)	420	200	630	
Male	400.98 (79.53)	416	200	560	
Female	416.28 (73.91)	427	241	630	
Random blood glucose (mg/dL)					0.247
Total	127.79 (54.25)	109	61	400	
Male	133.98 (66.54)	108	70	400	
Female	121.59 (37.93)	111	61	254	
Serum cholinesterase (units per liter)					0.605
Total	3207.16 (2862.13)	841	50	11705	
Male	3284.24 (2778.22)	581	50	10630	
Female	3157.92				

	(2946.28)	1067	123	11705	
White blood cell (per cubic millimeter)					0.240
Total	13224.04 (5956.92)	12000	1100	36000	
Male	14384.61 (6014.17)	12950	5400	29000	
Female	12063.46 (5722.64)	11750	1100	36000	
amount of organophosphate consumption (milliliters)					0.042
Total	151.40 (149.29)	100	3	1000	
Male	186.80 (192.65)	200	5	1000	
Female	113.76 (86.33)	100	3	300	
time interval between exposure and hospital admission (hour)					0.557
Total	4.42 (3.85)	3	1	26	
Male	4.21 (4.15)	3	1	26	
Female	4.63 (3.57)	3	1	16	

Abbreviations: SD, standard deviation; Msec, milliseconds; mg/dL, milligrams per deciliter.

Regarding random blood glucose levels at admission, the mean level was 127.79 ± 54.25 milligrams per deciliter, with the lowest value at 61 milligrams per deciliter and the highest at 400 milligrams per deciliter (Table 1). Ninety-five individuals (91.3%) had blood glucose levels within the normal range, one individual (0.9%) had low blood glucose (below 70 mg/dL), and eight individuals (7.7%) had high blood glucose (above 200 mg/dL).

Upon admission, the mean serum cholinesterase level was 3207.16 ± 2862.13 units per liter, with values ranging from a minimum of 50 units per liter to a maximum of 11705 units per liter (Table 1). Twenty-nine individuals (27.9%) had serum cholinesterase levels within the normal range, while 75 individuals (72.1%) exhibited lower levels.

The average white blood cell (WBC) count was 13224.04 ± 5956.92 per cubic millimeter, with a range from 1100 to 36000 (Table 1).

Men demonstrated a higher average consumption of OP than women. The mean volume of poison ingested in this study was 151.4 ± 149.3 milliliters, with the smallest amount being approximately half a tablespoon (around 3 milliliters) and the largest amount being 1 liter (Table 1). The precise dosage ingested was not determined in 30 patients (28.8%) and was categorized as unknown.

The mean time interval between exposure and hospital admission was 4.42 ± 3.85 hours, with the shortest time being 1 hour and the longest time being 26 hours.

No significant statistical relationships were observed between factors such as age, gender, marital status, place of residence, level of education, volume of OP consumed, time of hospital admission, and white blood cell count in relation to either QTc interval or blood glucose levels ($P > 0.05$). The mean blood glucose level of the patients was 127.78 ± 54.25, with a statistically significant negative correlation noted between blood glucose level and serum cholinesterase level; as serum cholinesterase levels decreased, blood glucose levels increased ($P = 0.046$, Pearson Correlation = -0.196). Additionally, *t*-test analysis showed that patients with normal cholinesterase levels had an average blood glucose level of 109.55 ± 27.98, whereas those with low cholinesterase levels had an average of 134.84 ± 60.16, a difference that was statistically significant ($P = 0.004$). All eight patients with high blood glucose levels above 200 and one with low blood glucose below 70 had reduced cholinesterase levels.

t-test analysis revealed that patients with low cholinesterase levels had a slightly higher mean QTc interval (413.01 ± 83.37) compared to those with normal levels (397.31 ± 56.00), although this difference was not statistically significant ($P = 0.271$). Moreover, no significant correlation was found between the mean QTc interval and mean serum cholinesterase level ($P = 0.466$, Pearson Correlation = -0.072). Analysis of variance indicated that the mean serum cholinesterase level was 2537.57 ± 2034.09 in patients with low QTc interval, 4042.47 ± 3504.09 in those with normal QTc interval, and 2090.48 ± 1313.95 in patients with long QTc interval. Statistically significant differences were observed between patients with low and normal QTc intervals ($P = 0.035$) and between normal and high QTc intervals ($P < 0.001$). However, no significant difference was found between patients with low and high QTc intervals ($P = 0.686$). Additionally, *t*-test analysis determined that patients with abnormal QTc intervals (either lower or higher than normal) had significantly lower serum cholinesterase levels (2268.72 ± 1587.61) ($P < 0.001$).

5. Discussion

In this study, we examined all patients poisoned with organophosphorus compounds who were admitted to Sina Medical Center in Tabriz in 2016 and 2017. Out of 238 OP poisoned patients (125 males and 113 females), 104 were selected for inclusion in the study after applying the exclusion criteria. In comparison, the study by Jeong Mi Moon et al. reported 123 patients (66.8%) were male and 61 patients (33.2%) were female (3). Similarly, the study by Kang et al. found that 38 patients (56%) were male and 30 patients (44%) were female (8). The initial

statistics of our study show a nearly equal gender distribution, suggesting that both genders have relatively easy access to OP poisons in developing countries, particularly in Iran, due to insufficient regulation over the sale and use of pesticides.

The mean age of patients in our study was 30.81 ± 15.04 years. This contrasts with the findings of Moon et al., where the average age was 16.6 ± 2.59 years (3), and Kang et al., who reported an average age of 54.5 years (8). Shahin Shadnia et al. noted an average age of 29.31 ± 10.2 years in their research (5). Comparing these figures, it appears that the average age of OP poisoning victims in Iran is somewhat younger than in other studies. Consequently, without prompt and appropriate treatment, these individuals face a higher potential for years of life loss. This highlights the critical need for rapid and effective therapeutic interventions, access to essential toxicology laboratory resources, suitable antidotes, and efforts by authorities to restrict easy access to poisons in Iran.

Regarding the intent behind the poisoning, our study found that 81 individuals (77.9%) ingested poisons with suicidal intent, while 23 individuals (22.1%) did so accidentally or unintentionally. Akdur et al. reported that 74.07% of their patients ingested poisons with suicidal intent (1). Consistent with prior research, the majority of OP poisoning incidents are intentional, with individuals obtaining and using poisons for the purpose of suicide.

This study identified a significant statistical correlation between blood glucose levels and serum cholinesterase levels, aligning with other research that found a notable link between elevated blood glucose levels and the severity of OP poisoning, independent of cholinesterase levels (3, 8, 11). This suggests that abnormal blood glucose levels correlate with reduced cholinesterase levels and an increased risk of mortality and severe symptoms in OP poisoning cases.

In analyzing the QTc interval from patients' electrocardiograms, the mean value was 408.63 ± 76.79 milliseconds, with 31 individuals exhibiting long QT intervals. This finding indicates a potential risk of QT interval prolongation in these patients, a result that corroborates findings from other studies (1, 5). Unlike those studies, however, our research noted both prolonged and shorter than normal QT intervals. Various cardiac manifestations associated with OP poisoning, such as prolonged QTc interval, polymorphic ventricular tachycardia, ST-T changes, and cardiac conduction system irregularities, have been documented in several studies (1-5, 8-10, 12). Although the precise causes of these cardiac manifestations remain unclear, increased sympathetic and parasympathetic activity, hypoxia, acidosis, electrolyte imbalances, and the direct impact of the toxin on cardiac tissues are proposed as possible mechanisms (13, 14). Given the critical nature of cardiac complications in these patients and the potential for progression to more complex arrhythmias, regular monitoring, and cardiac surveillance are recommended for individuals with prolonged QTc intervals, especially since they also exhibited lower serum cholinesterase levels.

While other studies have highlighted an increased mortality risk in patients with long QT intervals (15, 16), our study did not record any deaths due to OP poisoning. Although relying solely on a single prognostic factor may be inadequate, the measurement of the QTc interval, according to other research, holds predictive value for poisoned patients (1, 5, 15, 16). In line with this, our findings show that patients with abnormal QT intervals, particularly those with long QT intervals, had significantly lower serum cholinesterase levels, underscoring the importance of this diagnostic test in assessing OP poisoning severity.

5.1. Conclusions

This study demonstrated a significant association between QTc interval and blood glucose levels with serum cholinesterase levels. Serum cholinesterase levels were found to decrease as QTc interval and blood glucose levels increased. Notably, patients with a QTc interval greater than 440 milliseconds or random blood glucose levels above 200 milligrams per deciliter exhibited significantly lower serum cholinesterase levels.

5.2. Study Limitations

While the increased number of exclusion criteria in the study contributed to greater accuracy, a potential limitation of the study design was the reduced sample size.

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Footnotes

Authors' Contribution: Study concept and design: Ali Banagozar Mohammedi, Maryam Zaare Nahandi, Ahad Banagozar Mohammedi. Acquisition of data: Mahdi khodayari, Amin Azimi: Interpretation of data: Mahdi khodayari, Amin Azimi, Ali Ostadi, Ali Banagozar Mohammedi. Drafting of the manuscript: Ali Banagozar Mohammedi, Maryam Zaare Nahandi. Critical revision of the manuscript for important intellectual content: Ahad Banagozar Mohammedi. Statistical analysis: Alireza Ghaffari, Mahdi khodayari , Amin Azimi. Administrative, technical, and material support: Ali Ostadi, Alireza Ghaffari. Study supervision: Ali Banagozar Mohammedi, Maryam Zaare Nahandi

Conflict of Interests: The authors declare that they have no conflict of interest. Personal or professional relations with organizations and individuals (parents and children, wife and husband, family relationships, etc.): Maryam Zaare Nahandi(wife)-Ali Banagozar Mohammadi(husband), Ahad Banagozar Mohammadi(Brother).

Data Availability: The dataset presented in the study is available on request from the corresponding author during submission or after publication.

Ethical Approval: This study is approved under the ethical approval code of "IR.TBZMED.REC.1397.378 ".

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