GLYCEMIC STATUS AS A PREDICTOR FOR THE OUTCOMES IN PATIENTS WITH ACUTE ORGANOPHOSPHORUS PESTICIDES POISONING

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ABSTRACT

Background: Acute organophosphate (OP) toxicity is a major health problem in different populations. Nearly three million cases are affected annually all over the world. The most common clinical presentations include muscarinic, nicotinic, and central nervous system manifestations resulting from cholinergic overload. Nevertheless, endocrine toxicity and affection of glucose homeostasis are reported. **Objectives:** The current study **aimed to** study random blood sugar (RBS) as a simple, inexpensive tool to predict mortality and major outcome events in acute organophosphate poisonings. **Patients & methods:** Ninety adult patients with acute organophosphate poisoning were included in the study. Patients already known to be diabetic before exposure and those with mixed intoxication were excluded. RBS was done to all included patients on admission before receiving any medications. **Results:** Patients were categorized into euglycemic (62.2%), hyperglycemic (28.9%), and hypoglycemic (8.9%). The severity of organophosphorus poisoning symptoms and signs was graded into; Mild (32.2%), Moderate (38.9%), and Severe (28.9%) grades with a statistically significant association between RBS and poisoning severity at the time of admission. In addition, RBS showed a statistically significant association with each of serum cholinesterase levels, the delay time before hospital admission, the need for intubation, mechanical ventilation, and death. Meanwhile, RBS had no statistically significant association with either dose of atropine & toxogonine or the duration of hospital stay. **Conclusion:** It could be concluded that random blood sugar on admission in acute organophosphorus poisoned patients is a simple, cheap, and reliable marker that may help to predict the clinical severity and outcomes.

Keywords: Acute Organophosphate Toxicity, random blood sugar (RBS), Ventilation, Mortality.

INTRODUCTION

Organophosphates are esters of phosphoric acid designed for pest control both in agriculture and household gardens **(Kharel et al., 2020).** Globally, these heterogeneous compounds constitute a common accidental health hazard. Easy availability and low cost make them one of the most commonly used suicidal poisons, especially in developing countries **(Afify et al., 2016a; Dungdung et al., 2020).** Worldwide, acute organophosphorus pesticide poisoning registered a high prevalence, affecting about 3 million people, with 300 000 deaths annually **(Geetha Rani et al., 2020).**

Organophosphate toxicity is mediated through covalent phosphate binding to cholinesterase's active sites rendering them enzymatically inert **(Afify et al., 2016b; Oliveira et al., 2019).** Afterward, initial overstimulation of the central nervous system, cholinergic synapses, together with neuromuscular junctions, takes place. This

is followed by central and peripheral paralysis. Subsequently, Muscarinic, nicotinic, and central nervous system manifestations will result from cholinergic overload **(Elagamy & Gabr, 2019).**

In addition, organophosphate induces disruption of cellular oxidative balance, immunotoxicity, reproductive toxicity, and genotoxicity. Furthermore, endocrine toxicity and glucose homeostasis are affected **(Raveendra et al., 2020).** Moreover, a variety of glycemic states ranging from hypoglycemia to hyperglycemia, and rarely ketoacidosis can be reported **(Kurtoglu, 2019).**

In animal studies**, Panda et al. (2015)** have registered increased cholinergic activities due to hyperglycemia, together with hyperglycemic changes during anticholinesterase poisoning. In human research, **Raghapriya et al., 2018** suggested an association between glycemic state and morbidity, mortality, and mechanical ventilation assistance.

Predicting outcome in critically ill patients is a key component and a major concern in any health care system. At the same time, acute organophosphate toxicity still a big problem with major consequences, together with a striking lack of recent Egyptian studies regarding random blood sugar (RBS) as a predictor of acute organophosphate toxicity. Hereafter, the current study aimed to use RBS as a simple, inexpensive tool to predict mortality and major outcome events in acute organophosphate poisonings.

PATIENTS AND METHODS

This study is a prospective cross-sectional study. It was carried out following the approval of the medical research ethical committee of Tanta Faculty of Medicine on patients admitted to Tanta Poison Control Center, Tanta Emergency University Hospital with acute organophosphorus poisoning throughout the period from the 1st of September 2019 to the 31st of August 2020.

All included patients or guardians (if the patients were unable to participate in the consent process) were asked to provide informed written consent for participation after receiving detailed information about the study. Data confidentiality, including the results of investigations, was maintained by making code numbers for every patient (available for main investigator only), data were analyzed anonymously.

Adult patients acutely exposed to organophosphate were included in the study. Patients who were known to be diabetic before exposure or with abnormal Hb and/or Hb A1c levels were excluded. Moreover, patients with chronic renal disease, chronic pancreatic disease, chronic liver disease, alcoholics, and pregnant females were excluded. Additionally, patients admitted with mixed intoxication or associated trauma, and those who received any medications before admission were excluded from the study.

Diagnosis of organophosphorus poisoning was based on the history of exposure, the presence of organophosphorus symptoms and signs, clinical improvement after administration of atropine and oximes (toxogonin), and the decrease in serum cholinesterase enzyme levels **(Tsai et al., 2007 and El-Ebiary et al., 2016).**

Demographic data (including age, gender, occupation, and residence) and Toxicological data (including the route of exposure and manner of poisoning) were reported for all included cases.

The severity of symptoms and signs of acute OPP was graded according to **Minton & Murray (1988)** into **Mild OPP;** headache, blurred vision, dizziness, fatigue, nausea, vomiting, excessive sweating, salivation, abdominal pain, and tightness in the chest**. Moderate OPP;** Symptoms of mild poisoning in addition to muscular fasciculation, weakness, inability to walk, chest crepitations, and miosis. **Severe OPP**; Symptoms of moderate poisoning in addition to unconsciousness,

flaccid paralysis, respiratory distress, cyanosis, and marked miosis with loss of pupil reflexes.

Blood samples were collected at the time of admission before administrating any medication under complete aseptic conditions. Two milliliters of venous blood were kept into a clean, dry tube and left standing for a few hours before centrifugation to avoid hemolysis. Serum was separated and then used to estimate both serum cholinesterase level and random blood glucose.

Serum cholinesterase level was measured using butyrylthiocholine substrate, commercial kit supplied by Biodiagnostic, Egypt (normal value 5400-13200 U/L) **(Kende and Bottger 1967; Blawen et al., 1983)**. Random blood sugar level was determined according to **Trinder (1969) and Sharp (1972)** by glucose oxidase method. Blood collection syringes, tubes, and body fluids (blood samples) were safely disposed of for infection control and to avoid any risk of environmental pollution.

Based on RBS levels at the time of admission, patients were categorized into three groups; hypoglycemic with RBS less than 70 mg/dL, euglycemic (70-140 mg/dL), and hyperglycemic with RBS exceeding 140 mg/dL **(Raveendra et al., 2020).**

Statistical analysis was performed using Statistical Package for Social Sciences (IBM SPSS Statistics) for Windows, version 26 (IBM Corp., Armonk, NY, USA). For quantitative data, assessment of distribution was performed using the Shapiro-Wilk test for normality and visual assessment of graphs.

For normally distributed data, variables were summarized as mean ± standard deviation (SD). Comparison between the three studied groups was carried out using the One-way ANOVA test (followed by Tukey posthoc test if ANOVA yielded significant p-value).

For abnormally distributed data, the variables were summarized as the median and interquartile range (IQR, expressed as 25^{th} – 75^{th} percentiles). Comparison between the three studied groups was carried out using Kruskal-Wallis (KW) test (followed by Dunn-Bonferroni posthoc test if KW yielded a significant p-value).

Correlation between numerical variables was studied using Spearman's rank-order correlation. Spearman's correlation coefficient (r_s) measured the direction and strength of the correlation. A coefficient ≤0.39 is considered weak, 0.40 – 0.96 is moderate, and ≥0.7 is strong **(Schober et al., 2018).** A p-value ≤0.05 was adopted for interpretation of statistical tests.

RESULTS

During the study period, 90 patients presenting with acute organophosphorus poisoning fulfilled the inclusion and exclusion criteria. The mean age of included patients was 36.1±13.2, with a predominance of males (81.1%). Sociodemographic characteristics of participant patients are illustrated in **table (1).**

Table (2) demonstrates the toxicological and clinical data of studied patients. Patients were categorized into euglycemic (62.2%), hyperglycemic (28.9%), and hypoglycemic (8.9%). Eighty patients (88.9%) were improved and discharged; meanwhile, ten patients ended up with death. Intubation and mechanical ventilation were required in 13.3% of included patients.

Sociodemographic data, route, and manner of poisoning registered no significant association with random blood sugar on admission. Meanwhile, delay time before hospital admission revealed a significant association with random blood sugar on admission **(Table 3).** Furthermore, Spearman's rank-order correlation showed that there was a significant positive correlation between random blood sugar and delay time before hospital admission (r_s=0.220, p = 0.037).

On admission, both severities of poisoning and serum cholinesterase levels

had a significant association with RBS **(Table 4).** Spearman's rank-order correlation declared that there was a significant positive correlation between random blood sugar and severity of poisoning (r_s=0.385, p<0.001). A significant negative correlation existed between random blood sugar and serum cholinesterase level (r_s=-0.337, p = 0.001).

Table (4) illustrates that RBS had no significant association with atropine & toxogonin doses and duration of hospital stay. On the other hand, there was a significant association between RBS and both need for mechanical ventilation and death.

Table (1): Sociodemographic data of organophosphate poisoned patients (N=90)

Age				**Gender**				**Residence**			
Min.	Max.	St.dev.	Mean	Male		Female		Urban		Rural	
				N.	%	N.	%	N.	%	N.	%
18.0	65.0	13.2	36.1	73	81.1%	17	18.9%	25	27.8%	65	72.2%
Occupation											
Employed						Unemployed					
Employed		Farmer		Skilled worker		Housewife		unemployed		Student	
N.	%	N.	%	N.	%	N.	%	N.	%	N.	%
7	7.8%	52	57.8%	7	7.8%	11	12.2%	7	7.8%	6	6.7%

N: number - Min: minimum – Max: maximum - St.dev: standard deviation.

Table (2): Toxicological and clinical data of organophosphate poisoned patients (N=90)

Manner of poisoning				**Pre-hospitalization period (hours)**				**Route of poisoning**			
Accidental		Suicidal		Min	Max.	Median	IQR	Ingestion		Combined	
No.	%	No.	%					No.	%	No.	%
56	62.2%	34	37.8%	1.0	24.0	4.0	2.0 – 8.0	38	42.2%	52	57.8%
Organophosphorus poisoning severity						**Cholinesterase level**					
Mild		Moderate		Severe		Min.	Max.	Median		IQR	
No.	%	No	%	No.	%						
29	32.2%	35	38.9%	26	28.9 %	89.0	11485.0	2411.0		1161.0 - 3480.0	
Number of Atropine ampoules						**Number of Toxogonin ampoules**					
Min.	Max.	Median	IQR			Min.	Max.	Median		IQR	
1.0	88.0	10.0	5.0 - 13.0			1.0	28.0	4.0		4.0 - 7.0	
Period of hospital stay						**Random blood sugar**					
Min.	Max.	Median	IQR			Normal		Hypoglycemic		Hyperglycemic	
0.25	10.0	2.0	2.0 - 3.0			No.	%	No.	%	No.	%
						56	62.2%	8	8.9%	26	28.9%
Outcome											
Improved & discharged				Intubation & Mechanical ventilation				Mortality			
N.		%		No.		%		No.		%	
80		88.9%		12		13.3%		10		11.1%	

N: number - Min: minimum – Max: maximum - IQR: Interquartile range

Table (3): Comparison between groups of RBS status as regards relevant sociodemographic and toxicological data (N = 90)

		Euglycemia		Hyper-glycemia		Hypo-glycemia		Total		Test statistic	p
Age (years)	Range Mean ± SD	18 – 65 35.3 ± 12.9		18 – 60 40.2 ±13.9		19 – 45 28.9 ± 10.9		18 – 65 36.1 ± 13.2		2.623 [a]	0.078
Gender	Female	8	47.1%	6	35.3%	3	17.6%	17	100%	3.078 [b]	0.213
	Male	48	65.8%	20	27.4%	5	6.8%	73	100%		
Residence	Urban	4	16.0%	17	68.0%	4	16.0%	25	100%	4.133 [b]	0.125
	Rural	4	6.2%	39	60.0%	22	33.8%	65	100%		
Occupation	Employed	4	6.1%	44	66.7%	18	27.3%	66	100%	3.279 [b]	0.185
	Unemployed	4	16.7%	12	50.0%	8	33.3%	24	100%		
Manner of poisoning	Accidental	39	69.6%	13	23.2%	4	7.1%	56	100%	3.551 [b]	0.171
	Suicidal	17	50.0%	13	38.2%	4	11.8%	34	100%		
Route of poisoning	Ingestion	4	10.5%	21	55.3%	13	34.2%	38	100%	1.445 [b]	0.516
	Combined	4	7.7%	35	67.3%	13	25.0%	52	100%		
Delay time before hospital admission (hours)	Range Median IQR	1 – 24 4 2 - 6		1.5 – 20 5 4 - 10		1 – 10 2 1 - 6.5		1 - 24 4 2 – 8		6.149 [c]	0.051*

a: One way ANOVA - b: Fisher-Freeman-Halton exact test - c: Kruskal-Wallis test - * significant at p ≤ 0.05 - IQR: Interquartile range

Table (4): Comparison between groups of RBS status as regards clinical data and outcomes (N = 90)

		Euglycemia		Hyperglycemia		Hypoglycemia		Total		Test statistic	P
		N	%	N	%	N	%	N	%		
Severity of toxicity	Mild	26	89.7	2	6.9	1	3.4	29	100	16.781 [b]	0.001*
	Moderate	19	54.3	11	31.4	5	14.3	35	100		
	Severe	11	42.3	13	50	2	7.7	26	100		
ChE (U/L)	Range Median IQR	89 - 11485 2499 1347 - 3500		451 - 11169 1186.5 945 - 2760		2600 - 3930 3334.5 2767 – 3815		89 - 11485 2411 1161 - 3480		10.580 [a]	0.005* p1=0.057 p2=0.244 p3=0.008*
Atropine (ampule)	Range Median IQR	2 - 79 10 5 – 13		1 – 88 7.5 5 – 13		3 - 12 7 4 – 10		1 – 88 10 5 – 13		1.855 [a]	0.396
Toxogonin (ampule)	Range Median IQR	4 - 11 4 4 – 8		1 - 28 4 4 – 7		4 - 4 4 4 – 4		1 – 28 4 4 – 7		1.185 [a]	0.553
Hospital Stay (days)	Range Median IQR	0.5 - 6 2.5 2 – 3		0.3 - 10 2 1 – 4		1 - 3 2 2 – 2		0.25 – 10 2 2 – 3		1.957 [a]	0.376
Tube	No	52	66.7%	18	23.1%	8	10.3%	78	100%	8.114 [b]	0.016*
	Yes	4	33.3%	8	66.7%	0	0%	12	100%		
Ventilation	No	54	66.7%	19	23.5%	8	9.9%	81	100%	9.371 [b]	0.006*
	Yes	2	22.2%	7	77.8%	0	0%	9	100%		
Mortality	Survived	54	67.5%	18	22.5%	8	10%	80	100%	11.639 [b]	0.002*
	Non-survivor	2	20%	8	80.0%	0	0.0%	10	100%		

N: number a: Kruskal-Wallis test - b: Fisher-Freeman-Halton exact test - * significant at p ≤ 0.05 - IQR: Interquartile range

DISCUSSION

Acute organophosphorus pesticide poisoning is a serious clinical problem in many countries with high mortality. The present study was designed to evaluate the effectiveness of RBS at the time of admission as a predictor for the outcomes of organophosphorus poisoned patients. In order to achieve this target, sociodemographic, toxicological, clinical data, and outcomes were analyzed against RBS findings in acute organophosphorus poisoned patients.

The results of sociodemographic characteristics, toxicological data, and clinical findings obtained in this study were comparable to results gathered from different poison control centers in Egypt and across the developing world **(Panda et al., 2015; Abd El al et al., 2016; Elagamy & Gabr, 2019 and Reddy et al., 2020).**

Anticholinesterase-induced hyperglycemia has been explained by excess ACTH and catecholamine release after continuous cholinergic stimulation (**Sudhir et al., 2013).** According to **Xiao et al. (2017)**, increased glycogen breakdown together with pancreatitis could be contributing factors of anticholinesterase-induced hyperglycemia.

Based on these reports, registering 26 hyperglycemic patients in the current study is reasonable. Furthermore, a significant positive correlation between RBS and delay time before hospital admission was recorded. A result that is totally in agreement with **Sudhir et al. (2013),** who proposed the stress of delayed treatment as a contributor to adrenaline gush and associated hyperglycemia**.**

A significant positive correlation between hyperglycemia and severity of poisoning was recorded in the present study. This finding was supported by **Panda et al. (2015)** and **Raveendra et al. (2020)**, who reported a severe grade of poisoning in hyperglycemic patients. In addition, the grade of poisoning was found to be exaggerated by hyperglycemia and vice versa in both animal **(Liu et al., 2007)** and human studies **(Raghapriya et al., 2018).**

Such a positive correlation could be explained by the over-stimulation of nicotine receptors present on sympathetic ganglia leading to excess release of catecholamines from adrenal medulla. Moreover, severe cholinergic stimulation could increase ACTH release from the anterior pituitary. In addition, increased glycogenolysis and gluconeogenesis also contribute to this increase **(Sudhir et al., 2013 and Panda et al., 2015).**

Since depression of serum cholinesterase level is directly correlating with severity of organophosphorus poisoning **(Elagamy & Gabr, 2019)**, and the current study revealed a significant positive correlation between severity of organophosphorus poisoning and RBS of patients. It was expected to find a significant negative correlation between serum cholinesterase level and RBS in the present study. This finding agreed with **Rao & Raju (2016) and Raveendra et al. (2020)**, who recorded that hyperglycemia on admission directly correlates with depression of serum cholinesterase levels in organophosphorus poisoned patients.

In the present study, atropine & toxogonin doses and duration of hospital stay registered no significant association with RBS. This finding was contradictory to **Panda et al. (2015) and Raveendra et al. (2020)**, who reported a significant positive association between RBS of acute organophosphorus poisoned patients and the total dosage of atropine, toxogonin, and duration of hospital stay. Such inconsistency of result could be attributed to the difference in the number of severe cases in each study, along with variations in atropine & toxogonin doses in treatment protocols among poison control centers.

There was a significant association between RBS and both mortality and need for mechanical ventilation (80% and 77.8% of mortalities and ventilated patients respectively were hyperglycemic) in the present study. This result is in

accordance with **Raghapriya et al. (2018) and Raveendra et al. (2020).** This could be explained considering the significant positive correlation between hyperglycemia and the severity of poisoning recorded in the present study.

CONCLUSION

It could be concluded that random blood sugar on admission in acute organophosphorus poisoned patients is a simple, cheap, and reliable marker that may help to predict the clinical severity and outcomes. To the best of the authors' recent knowledge, the current study is the first to investigate RBS as a predictor of mortality and the need for ventilation in acute organophosphate poisoned patients in Egypt.

RECOMMENDATION

Further research on larger scales are needed to investigate the glycemic state as a predictor for cholinergic toxicity outcomes.

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الملخص العربى

مستوي السكر في الدم كمتنبئ للنتائج في مرضى التسمم الحاد بمبيدات الآفات الفسفورية

يعد التسمم الحاد بمبيدات الفوسفور العضوي من المشكلات الصحيه الخطيرة المنتشره في العديد من المجتمعات حول العالم، حيث تؤثر سلبا على ما يقرب من ثلاثة ملايين من الأشخاص سنويا. وتظهر الإصابه بهذا التسمم بصور متعددة الأعراض أشهرها ينتج عن تحفيز للنهايات العصبيه الكولينية، والوصلات العصبية العضلية والجهاز العصبي المركزي. بالإضافة إلى ذلك قد تحدث اضطرابات في وظائف عدد من الغدد بالجسم مما يؤثر علي مستويات بعض الهرمونات ومستويات السكر في الدم. ولذلك كان الهدف من الدراسة الحالية هو الكشف عن إمكانية إستخدام مستوي السكر في الدم (وقت دخول المستشفي وقبل التدخل الطبي) كمؤشر للتنبؤ بنتائج التسمم الحاد بمبيدات الفوسفور العضوي. وقد تضمنت الدراسه تسعون مريضا بالغا من المصابين بالتسمم الحاد بمبيدات الفوسفور العضوي. وذلك بعد استبعاد أولئك المصابين بمرض البول السكري من الدراسه. وبناءا على نتائج الدراسه تم تصنيف المرضي إلى ثلاث مجموعات وفقا لمستوى السكر في الدم وقت الدخول للمستشفي حيث كان طبيعيا في 62.2٪ منهم، ومرتفعا في 28.9٪، ومخفضا عن المستوي الطبيعي فقط في 8.9٪ من المرضي محل الدراسه. كما تم تصنيف الحالات المتضمنه في الدراسه بناءا على شدة أعراض التسمم إلى؛ درجات خفيفة (32.2%) ومتوسطة (38.9%) ومرتفعة (28.9%) مع وجود ارتباط ذي دلالة إحصائية بين مستوي السكر بالدم وشدة التسمم وقت دخول المستشفي. بالإضافة إلى ذلك، تبين وجود علاقة ذات دلالة إحصائية لمستوي السكر بالدم مع كل من مستويات الكولينستريز في الدم، والوقت المنقضي قبل الوصول للمستشفى، والحاجة إلى تركيب أنبوبه حنريه مع أو بدون تنفس صناعي، وحدوث الوفاة في حين أنه لم يتضح وجود علاقة ذات دلالة إحصائية بين مستوي السكر بالدم وأي من مدة العلاج بالمستفي أو جرعات العلاجات الماده للتسم المستخدمه (أتروبين و تكسوجونين).