Prognostic Value of Long Corrected QT Interval on Electrocardiogram in Acute Organophosphate Poisoning: A Cohort Study

JAYSHREE GAMIT[1], ARCHANA GANDHI[2]

ABSTRACT

Introduction: According to data available from National Poison Information Centre India, suicidal poisoning with household agents (organophosphates, carbamates etc.,) is the most common modality of poisoning. There are reports suggesting relationship between prolonged corrected QT interval and the severity of Organophosphate (OP) poisoning. Corrected QT (QTc) interval is measured in 12 lead electrocardiograms taken on admission.

Aim: To assess prognosis of acute organophosphate poisoning patients by studying association of corrected QT interval with its complications and mortality.

Materials and Methods: The present cohort study was conducted at Medicine Department of Medical College, Baroda and Sir Sayaji General Hospital, Vadodara, Gujarat, India, from December 2017 to November 2018. The study included 60 patients with a history of OP poisoning. The QTc interval in electrocardiogram was determined by using the Bazett formula. Prognostic importance of QTc interval was assessed by correlating it with Paradeniya Organophosphorus Poisoning Scale score, hospital stay, atropine requirement, requirement of ventilatory support and mortality. Data was analysed by using descriptive statistics and Chi-square test.

Results: The organophosphate poisoning was seen more in younger age group, between 18-29 years (68.4%). The QTc

prolongation was seen in 12 (80%) of patients in moderate grade of Paradeniya Organophosphorus Poisoning Scale and in 9 (20%) patients among mild grade of Paradeniya Organophosphorus Poisoning Scale (p-value=0.0001). Amongst patients who needed hospital stay for more than seven days, QTc prolongation was seen in 43% of patients, and in patients who needed hospital stay for less than seven days QTc prolongation was seen in 9% of patients (p-value=0.0223). Statistically significant association was seen between atropine ampule requirement and QTc prolongation. Total 29 (48.3%) patients developed respiratory depression, and amongst them 19 (65.5%) had QTc prongation (p-value <0.0001). Out of, 13 (22%) patients died and amongst them 12 (92.31%) had QTc prolngation. In those who survived 47 (78%) only 9 (19.15%) had QTc prolongation (p-value <0.0001).

Conclusion: Prolonged QTc interval in electrocardiogram is a good prognostic indicator in patients with organophosphorus poisoning. Early identification of prolonged QTc interval and subsequent timely shifting of patients to Intensive Care Unit (ICU) and subsequent intensive management in a patient of OP poisoning would be of profound value at any level of health care setting for favourable outcomes.

INTRODUCTION

Poisoning with organophosphorus compound is a global problem. World Health Organisation (WHO) estimates that one million serious unintentional poisonings occur every year and an additional two million people are hospitalised for suicide attempts with pesticides [1].

India is a predominantly agricultural country where pesticides and insecticides are routinely used for farming and access to these poisonous chemical substances by the population is easy. According to National Poison Information Centre India, suicidal poisoning with household agents is the most common modality of poisoning [2]. Official data of National Crime Records Bureau for 2020 suggest that 25% of total officially recored suicides in India's (1,53,052) were due to ingestion of poison [2].

Presently, organophosphates are one of the most widely used insecticides world over. Acute poisoning with these compounds is much more dangerous and necessitates emergency medical support. Pharmacological effects of organophosphate compounds are primarily due to prevention of hydrolysis of acetylcholine by acetylcholinesterase. Thus, acetylcholine acts for an excessively longer time, causing symptoms.

Prognosis of organophosphate poisoning can be determined by various clinical parameters like amount of poison ingested, Glasgow Coma Scale score, respiratory paralysis, duration of coma and biochemical markers like plasma cholinesterase and red cell acetyl cholinesterase activity [3-5]. Peradeniya Organophosphate Poisoning scale (POP scale) is scoring system where 5 clinical manifestations of OP Poisoning are selected as parameters and severity of poisoning assessed on that [5]. It becomes very difficult to know and rely on history about the amount of poison ingested. Respiratory paralysis and deterioration in consciousness may not be present in early phase. Categorisation of OP patients by POP score requires medical expert's eye and observation. Therefore, it is of paramount importance to identify prognostic parameter that is easy and reliable for patients of OP poisoning.

There are publications that found a relationship between prolonged corrected QT (QTc) interval and the severity of poisoning [6-9]. Corrected QT interval is measured in 12 lead electrocardiograms taken bedside. This study aimed to assess prognosis of acute organophosphorus poisoning by corrected QT interval and its association with complications and mortality of organophosphate poisoning patients.

MATERIALS AND METHODS

The present cohort study was conducted at Medicine Department of Medical College, Baroda and Sir Sayaji General Hospital, Vadodara, Gujarat, India, from December 2017 to November 2018. Permission of Institutional Ethics Committee was taken before starting the study (EC Reg No: ECR/85/Inst/GJ/2013/RR-16). Total 60 patients were included in the study.

Inclusion criteria: Patients with organophosphorus compound intoxication were included in the study.

Exclusion criteria: Patients with diabetes mellitus, documented heart disease, renal failure, respiratory disease, hepatic failure and electrolyte imbalance, ingestion with other agents and treatment taken from other medical centre before admission in SSG Hospital were excluded from the study.

Study Procedure

Age, gender, occupation, routes of exposure, intention of ingestion, compounds involved and presenting complaints like giddiness, vomiting, excessive salivation, lacrimation, altered sensorium, convulsion were noted at the time of admission. Thorough examination was done with special emphasis on cholinergic features like pinpoint pupils, excessive salivation, lacrimation and fasciculation. Routine blood investigations and serum cholinesterase levels were checked in all patients.

Bazett formula: Bedside 12 leads electrocardiogram was done on admission and corrected QT interval was counted by Bazett formula as below [10].

$$\text{Corrected QT interval} = \frac{\text{QT interval}}{\sqrt{(\text{RR interval})}} \quad (\text{RR Interval} = 60/\text{HR})$$

(QTc=Corrected QT interval, QTc prolongation considered in male >0.44 sec and in female is >0.46 seconds).

Peradeniya organophosphorus poisoning scale: Severity of Organophosphorus poisoning was graded as mild, moderate and severe as per POP scale which includes size of pupil, presence of fasciculation, respiratory rate and pulse rate, level of sensorium and presence or absence of seizures [11].

Patients were followed-up daily during indoor admission upto discharge or expiry. Complications like respiratory depression, convulsion, altered sensorium, hypotension, sudden cardiac arrest, arrhythmias and need for ventilator support were noted. Outcome was assessed based on days of hospital stay, total atropine dose requirement, ventilator support and mortality.

STATISTICAL ANALYSIS

All data was analysed in 60 patients by using descriptive statistics frequency, percentage, Chi-square test. A p-value <0.05 was considered significant. Data was entered in Microsoft excel sheet and analysed by using Epi Info™ software.

RESULTS

In the present study, the maximum prevalence of OP compound ingestion was in age group between 18-29 years (68.4%). Male and female patient ratio was 1.1:1 [Table/Fig-1]. Amongst 60 patients recruited in the study, 21 (35%) had prolonged QTc interval on electrocardiogram. There was no statistically significant association between age and QTc interval prolongation, as well as gender and QTc interval prolongation. A 15 (25%) patients presented 6 hours after exposure to OP compound and amongst them QTc prolongation was seen in 14 (93.33%) patients, only 15.56% patients had QTc prolongation amongst 45 patients who presented within 6 hours of exposure (p-value <0.0001).

As per the POP scale, 45 (75%) patients were in mild category, 15 (25%) in moderate category and no patient in severe category.

QTc prolongation was seen in 80% of patients of moderate category, whereas only in 20% of patients of mild category (p-value=0.0001) [Table/Fig-2].

Variables	QTc prolongation		Total	p-value
	Present	Absent		
Age group (years)				
18-29	13 (31.7%)	28 (68.3%)	41 (68.4%)	
30-39	4 (44.44%)	5 (55.56%)	9 (15%)	
40-49	3 (37.5%)	5 (62.5%)	8 (13.4%)	0.857
≥50	1 (50%)	1 (50%)	2 (3.33%)	
Total	21 (35%)	39 (65%)	60	
Gender				
Male	15 (46.88%)	17 (53.12%)	32 (53.4%)	0.073
Female	6 (21.43%)	22 (78.57%)	28 (46.6%)	
Time interval (Exposure to presentation)				
≤6 hrs	7 (15.56%)	38 (84.44%)	45 (75%)	**<0.0001**
>6 hrs	14 (93.33%)	1 (6.67%)	15 (25%)	

[Table/Fig-1]: Baseline characteristics and its association with QTc prolongation.
p-value <0.05 was considered as statistically significant

POP score	QTc prolongation		Total	p-value
	Present	Absent		
Mild	9 (20%)	36 (80%)	45 (75%)	
Moderate	12 (80%)	3 (20%)	15 (25%)	0.0001
Severe	-	-	-	
Total	21	39	60	

[Table/Fig-2]: Association OF QTc prolongation with POP score.
p-value <0.05 was considered as statistically significant

The total number of atropine required during treatment was between 11-100 ampules in 46 (77%) patients, followed by 101-200 ampules in 8 (13%) patients. Only 2 (3%) patients required >200 ampules of atropine. Amongst 8 patients who required 101-200 atropine ampules (60-120 mg atropine) QTc prolongation was seen in 7 (87.5%) patients and both two patients who required more than 200 atropine (120 mg) ampules had QTc prolongation (p-value=0.0011, Chi-square test). This suggests that patient with QTc prolongation required high atropine dose during treatment than the patient who had normal QTc in patients of OP poisoning [Table/Fig-3].

Number of atropine ampules	QTc prolongation		Total	p-value
	Present	Absent		
≤10 (6 mg)	1 (25%)	3 (75%)	4	
11-100 (6-60 mg)	11 (23.9%)	35 (76.1%)	46	0.0011
101-200 (60-120 mg)	7 (87.5%)	1 (12.5%)	8	
>200 (>120 mg)	2 (100%)	0 (0%)	2	

[Table/Fig-3]: Association of QTc with atropine requirement.
p-value <0.05 was considered as statistically significant

Amongst 33 patients who were discharged within 7 days, only 9% had QTc prolongation. Amongst 14 patients who required hospital stay of more than 7 days, QTc prolongation was seen among significantly higher number of patients (43%) [Table/Fig-4].

Days of hospital stay	QTc prolongation		Total	p-value
	Present	Absent		
≤7 Days	3 (9%)	30 (91%)	33	
>7 Days	6 (43%)	8 (57%)	14	**0.0223**
Total	9	38	47	

[Table/Fig-4]: Association of QTc prolongation with duration of hospital stay in discharged patients.
survived=47; p-value <0.05 was considered as statistically significant

Most common complication was respiratory depression (48.3%) which led to need for ventilatory support (48.3%), followed by altered sensorium (38.3%), and hypotension (21.7%). There was statistically significant association of complications of respiratory depression, ventilator requirement, altered sensorium and hypotension with QTc prolongation on ECG (p-value <0.0001) [Table/Fig-5]. Complications like convulsion, sudden cardiac arrest and acute kidney injury were recorded in 1 (1.7%), 1 (1.7%) and 3 (5%) patients only and so association with QTc prolongation could not be established for these complications. Arrhythmias were not documented in any patients so association of QTc with arrhythmia also could not be established.

In the present study, out of 60 patients, 47 (78%) patients survived and 13 (22%) patients died. Amongst 13 patients who died, 12 (92.31%) had prolonged QTc in ECG on admission (p-value <0.0001) [Table/Fig-5].

Complications	QTc prolongation present	QTc prolongation absent	Total	p-value
Respiratory depression				
Present	19 (65.5%)	10 (34.5%)	29 (48.3%)	<0.0001
Absent	2 (6.5%)	29 (93.5%)	31 (51.7%)	
Ventilatory support				
Present	19 (65.5%)	10 (34.5%)	29 (48.3%)	<0.0001
Absent	2 (6.5%)	29 (93.5%)	31 (51.7%)	
Hypotension				
Present	12 (92.3%)	1 (7.7%)	13 (21.7%)	<0.0001
Absent	9 (19.1%)	38 (80.9%)	47 (78.3%)	
Altered sensorium				
Present	16 (69.6%)	7 (30.4%)	23 (38.3%)	<0.0001
Absent	5 (13.5%)	32 (86.5%)	37 (61.7%)	
Outcome				
Mortality	12 (92.31%)	1 (7.69%)	13	<0.0001
Survived	9 (19.15%)	38 (80.85%)	47	

[Table/Fig-5]: Association of QTc prolongation with complications.
p-value <0.05 was considered as statistically significant

DISCUSSION

Organophosphates are frequently used pesticides which can lead to life threatening intoxication. All these compounds act by irreversible inhibition of Acetylcholinesterase (Ach). The clinical symptoms range from classical cholinergic syndrome to flaccid paralysis and seisures. Patients with history of OP ingestion can present at any level of health care setting like primary health centre, community health centre or tertiary care centre. There is an urgent need to identify patients who need urgent referral to tertiary care centre and prompt admission and intensive management in critical care unit. In the present study, authors aimed to assess association of prolonged QTc interval in bedside ECG taken on admission with various prognostic parameters.

To conclude present study, no association of QTc prolongation in OP poisoning patients with age and gender of patients was found. Shadnia S et al., also observed the similar results [8]. Patients who presented after 6 hours of exposure of OP compound, QTc interval prolongation was seen in majority of patients in the present study.

For OP compound poisoning Senanayake N et al., proposed POP scale for grading the severity of poisoning based on five cardinal manifestations which includes pupil size, respiratory rate, fasciculation, pulse rate, level of consciousness [11]. They found correlation between POP scores obtained on admission and three outcome variables, namely, death, the need for ventilatory support and the dose of atropine required were significant and so proposed that this score can be used for grading severity on first contact and predict possible outcomes in patients with OP intoxication. In the present study, patients with OP intoxication were graded as mild,

moderate and severe as per POP scale on admission. It was found that QTc prolongation in ECG taken on admission had significant association with severity of OP poisoning graded as per POP scale (p-value=0.0001). Similar findings were reported by Tripathy SK et al., [12].

Total number of atropine required ranged from less than 10 ampule (6 mg) to more than 200 ampule (120 mg) during hospitalisation. Patients who required more than 100 ampule i.e. 60 mg of atropine, 90% had QTc prolongation in ECG taken on admission. So, correlation between QTc prolongation in ECG and atropine requirement was significant in this study. Shadnia S et al., also found that higher atropine dose is required in patients with QTc prolongation [8].

In the present study, it was observed that majority of the patients who needed hospital stay for more than seven days had QTc prolongation against those who needed hospital stay for less than seven days. A similar observation was also seen in study done by Shadnia S et al., [8].

Most common complication found was respiratory depression (48.3%), chest excursion and single breath count, which led to need for ventilatory support (48.3%). Other complications found were altered sensorium (38.3%) and hypotension (21.7%). Association between QTc prolongation and respiratory depression, need for ventilatory support, hypotension and altered sensorium were statistically significant (p-value <0.0001). Tripathy SK et al., also observed significant association of QTc prolongation with respiratory failure (p-value <0.0001) [12].

In the present study, 22% mortality was observed, whereas, Shadnia A et al., observed 35.7% mortality and Tripathy SK et al., observed 10% mortality in their patients [8,12]. QTc prolongation had significant association with mortality of patients in the present study, and in study by Shadnia A et al., and Tripathy SK et al., [8,12].

Limitation(s)

Sample size was small. QTc interval was counted in electrocardiogram, done on admission. Changes in QTc interval in subsequent days was not studied.

CONCLUSION(S)

Identification of QTc interval prolongation in bedside ECG taken on admission of patients with OP compound intoxication has prognostic implication. Therefore, timely shifting of patients with QTc interval prolongation in bedside ECG to a tertiary care centre with critical care facility is of utmost importance. Continuous monitoring, intensive treatment and administration of atropine in adequate dosage in very early course of treatment is also of vital importance in patients of organophosphates intoxication with QTc prolongation in ECG.

REFERENCES

[1] Gunnell D, Eddleston M, Phillips MR, Konradsen F. The global distribution of fatal pesticide self-poisoning: Systematic review. BMC Public Health. 2007;7(1):357. Available from: https://bmcpublichealth.biomedcentral.com/articles/10.1186/1471-2458-7-357.

[2] National crime records bureau. Accidental deaths and suicides in India 2020. Chapter 2 Suicides in India; Available from: https://ncrb.gov.in/sites/default/files/adsi2020_Chapter-2-Suicides.pdf.

[3] Grmec S. Glasgow coma score and QTc interval in the prognosis of organophosphate poisoning. Acad Emerg Med. 2004;11(9):925-30. Available from: http://Doi.wiley.com/10.1197/j.aem.2004.03.018.

[4] Khan S, Kumar S, Agrawal S, Bawankule S. Correlation of serum cholinesterase and serum creatine phosphokinase enzymes with the severity and outcome of acute Organophosphate Poisoning: Study in rural central India. World J Pharmacy Pharmac Sci. 2016;5(4):1365-73.

[5] Rehiman S, Lohani SP, Bhattarai MD. Correlation of serum cholinesterase level, clinical score of presentation and severity of Organophosphorous Poisoning. J Nepal Med Assoc. 2008;47(170):47-52.

[6] Liu SH, Lin JL, Weng CH, Yang HY, Hsu CW, Chen KH, et al. Heart rate-corrected QT interval helps predict mortality after Intentional Organophosphate Poisoning. PLoS ONE. 2012;7(5):e36576. https://Doi.org/10.1371/journal.pone.0036576.

[7] Hodeib A, Khalifa H. Corrected QT interval as a predictor of outcomes in acute Organophosphate Poisoning cases. Ain Shams Journal of Forensic Medicine and Clinical Toxicology, 2020;34(1):34-40. Doi: 10.21608/ajfm.2020.68125.

[8] Shadnia S, Okazi A, Akhlaghi N, Sasanian G, Abdollahi M. Prognostic value of long QT interval in acute and severe organophosphate poisoning. J Med Toxicol. 2009;5(4):196-99. Doi: 10.1007/BF03178266. PMID: 19876851; PMCID: PMC3550412.

[9] Thakur DDK, Gaire DD, Jha DSD, Mahaseth DR. Qtc Prolongation as prognostic marker in Organophosphate Poisoning. International Journal of Medical Science and Clinical Invention. 2021;8(04):5317-37. Available from: https://Doi.org/10.18535/ijmsci/v8i04.01.

[10] Dahlberg P, Diamant UB, Gilljam T, Rydberg A, Bergfeldt L. QT correction using Bazett's formula remains preferable in long QT syndrome type 1 and 2. Ann Noninvasive Electrocardiol. 2021;26(1):e12804. Doi: 10.1111/anec.12804. Epub 2020. PMID: 33070409; PMCID: PMC7816807.

[11] Senanayake N, de Silva HJ, Karalliedde L. A scale to assess severity in organophosphorus intoxication: POP scale. Hum Exp Toxicol. 1993;12(4):297-99. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8104007.

[12] Tripathy SK, Rout PK, Debta N, Das S, Panigrahi M, Mishra SK, et al. Study of clinical profile of organophosphorus poisoning with special reference to electrocardiographic changes and electrolyte derangement. Int J Adv Med. 2018;5(1):50.

PARTICULARS OF CONTRIBUTORS:
1. Senior Registrar, Department of Medicine, Medical College, Baroda, Vadodara, Gujarat, India.
2. Associate Professor, Department of Medicine, Medical College, Baroda, Vadodara, Gujarat, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Archana Gandhi,
A/47, Sankheshwarnagar, Near AIR, Makarpura Road,
Vadodara-390009, Gujarat, India.
E-mail: draug20@gmail.com

AUTHOR DECLARATION:
• Financial or Other Competing Interests: None
• Was Ethics Committee Approval obtained for this study?   Yes
• Was informed consent obtained from the subjects involved in the study?   Yes
• For any images presented appropriate consent has been obtained from the subjects.   NA