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Research Article,

Qtc Prolongation as Prognostic Marker in Organophosphate Poisoning

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Summary:
The long QT syndrome (LQTS) is a disorder of myocardial repolarization characterized by a prolonged QT interval on the electrocardiogram (ECG). This syndrome is associated with an increased risk of polymorphic ventricular tachycardia, a characteristic life-threatening cardiac arrhythmia also known as torsades de pointes. A rate related corrected QT interval (QTc) can be calculated as QT/√RR and normally is ≤0.44s. Some references given QTc upper normal limits as 0.43s in men and 0.45s in female. OP compound supposed to block K+ channel and Na+/Ca++ channel and hence causing prolongation of QT interval. As we know that prolongation of QT interval may precipitate polymorphic ventricular tachycardia and sudden cardiac death, so it become important in case of OP poisoning and related mortality. In this study, I calculated corrected QT interval in diagnosed cases of OP poisoning admitted at Bir Hospital and compared QTc among those with complications and without complication. I also tried to evaluate QTc as a predictor for duration of hospital stays, ICU admission, vasopressor and mechanical ventilation requirement, higher POP score and low GCS.

Objectives: Purpose of this study is to find out QTc interval in diagnosed case of organophosphate poisoning and establish it as a prognostic marker.

Methodology:
This study is a hospital based cross-sectional observational study conducted at Bir-Hospital from 1st of March 2018 to 1st of February 2019. Altogether 66 patients below 75 years of age non-alcoholic without known co-morbidities admitted in general ward and ICU full filled inclusion criteria. They were enrolled in this study after taking informed consent. They were thoroughly examined and investigated. Specially ECG, CBC, RFT, LFT, PT/INR, ABG, Chest X-Ray, Serum ACHE done at treatment and during course of admission as per requirement. Personal and demographic parameters were recorded. Details of OP compound, amount ingested, duration of ingestion before presentation, total dose of atropinization, place of admission, complications developed during admission and duration of treatment were recorded. Patients were grouped into age class intervals, severity of poisoning done on the basis of ACHE level and POP score at admission. QTc calculated by Bazzet's formula, grouped into normal and prolonged categories. Statistical analysis was done by SPSS 20 and statistically significant tests were applied depending on type of variable as per need of this study.

Observation and Results:
Altogether 66 patients were enrolled in this study of which 44(66.7%) were female and 22(33.3%) were male. Maximum and minimum age of patients were 73 and 14-year-old with mean and SD of 33.03 and 12.921 respectively. Most of them were married (81.8%). Most of them were between age 20-40(56.06%). 50% of them had used diethyl and 50% had used dimethyl organophosphate compound. Among both group, 50% had used chlorpyrifos (50%) + cypermethrin

(5%). Severe poisoning is significantly higher in diethyl group (16.7% vs 1.5%) than in dimethyl group (fisher exact test, p = 0.005). vasopressor requirement (21.2% vs 7.6%) at Fisher exact test, p = 0.028 and complications developed (16.6% vs 4.5%) at Fisher exact test, p = 0.035 were significantly higher among diethyl group.

When considering 440ms as cut-off value for QTc, 44(66.7%) had normal QTc and 22(33.3%) had prolonged QTc. But when considering cut-off value of 430ms for male and 450ms for female, then 10(15.2%) male and 11(16.7%) female had prolonged QTc with total of 31.9%. Maximum and minimum QTc measured were 650.80ms and 370.50ms with respective mean and SD of 427.73 and 42.53. Mean QTc(464.85ms) among patient with POP score between 4-7(moderate poisoning) was significantly higher than those with POP score between 0-3(mild poisoning) whose mean QTc was 420.31ms[t(64) = -3.42, p = 0.001]. Mean QTc among patient with severe poisoning (ACHE = 0-700 U/L) was 446.09ms and among those with mild poisoning (ACHE = 1401-3500 U/L) was 438.94ms which was statistical insignificant [F (2,37) = 0.55, p = 0.581]. Mean QTc for patients with deranged LFT (mean = 490.33, SD = 82.44) was significantly higher than those with normal LFT (mean = 421.47, SD = 31.28) at t (64) = -4.27, p = 0.001. There was statistically significant association between QTc prolongation and vasopressor requirement [(X2(1) = 22.98, P<0.001]. While comparing with normal QTc group, prolonged QTc group has significantly higher rate of complications developed during course of treatment; ARDS (1.5% vs 0%), Aspiration pneumonia (7.6% vs 4.5%), bed sore (1.5% vs 0%), septic shock (3% vs 0%) [Fisher exact test, p<0.001]. One death was recorded who was a 40-year-old female with history of intake of 50ml of Chlorpyrifos (50%) + cypermethrin(5%) 12hour before presentation in Bir Emergency, dose of atropinization was 119ml, ACHE level was 600U/L, QTc recorded was 470.90ms. She was admitted in ICU for vasopressor and ventilator support.

Mean QTc for patients admitted in ICU (mean = 451.81, SD = 51.28) was significantly higher than those admitted in general ward (mean = 411.67, SD = 24.58) [t(64) = -4.31, p<0.001]. Prolonged QTc value predicted higher POP score with a significant regression equation of f(1,64) = 12.35, p = 0.001 with an R^2 of 0.162. A significant regression was also found when it was calculated to predict GCS based on QTc; b = -0.25, t(64) = 17.55, p<0.001 [f(1,64) = 4.155, p = 0.046 with an R2 of 0.061]. There was positive correlation between QTc level and amount of OP compound ingested at rs(66) = 0.466, p<0.01. Positive correlation was also found between QTc level and total dose of atropinization with rs(66) = 0.623, p<0.01.

Conclusion:

Patients with prolonged QTc have significantly higher POP score, lower GCS, long hospital stays, higher complications rate, more ICU requirement, and more vasopressors requirement. Hence QTc prolongation is a bad prognostic marker in organophosphate poisoning.Initial ECG must be obtained in emergency because one third of them associated with prolonged QTc interval.

Introduction:

The long QT syndrome (LQTS) is a disorder of myocardial repolarization characterized by a prolonged QT interval on the electrocardiogram (ECG). This syndrome is associated with an increased risk of polymorphic ventricular tachycardia, a characteristic life-threatening cardiac arrhythmia also known as torsades de pointes. The primary symptoms in patients with LQTS include palpitations, syncope, seizures, and sudden cardiac death. LQTS may be either congenital or acquired. These two primary syndromes (congenital and acquired LQTS) may be related, as some patients who develop acquired LQTS may have an inherited predisposition with abnormalities in repolarization that represent the forme fruste of LQTS. Acquired LQTS usually results from drug therapy, although hypokalemia, hypomagnesemia, and bradycardia can increase the risk of drug-induced LQTS.A rate related corrected QT interval (QTc) can be calculated as $QT/\sqrt{RR}$ and normally is ≤0.44s. Some references give QTc upper normal limits as 0.43s in men and 0.45s in female[11] Organophosphate compound supposed to block K+ channel and Na+/Ca++ channel and hence causing prolongation of QT interval. As we know that prolongation of QT interval may precipitate polymorphic ventricular tachycardia and sudden cardiac death, so it become important in case of organophosphate poisoning and related mortality.

Poisoning with organophosphorus (OP) compounds is a global public health problem. According to World Health Organization (WHO),

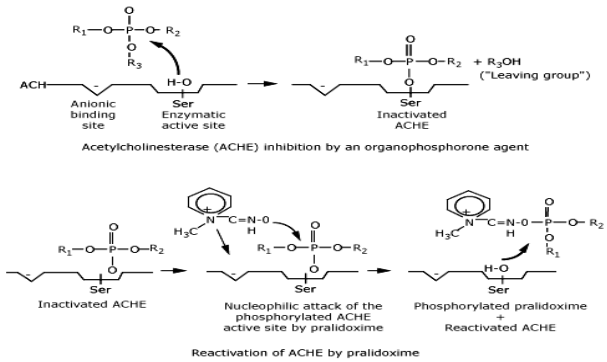
3 million cases of pesticide (mainly OP compounds) poisoning occur every year, resulting in an excess of 250,000 deaths. Of these, about 1 million are accidental, and 2 million are suicidal poisonings. The incidence has steadily increased in the recent past and has reached a level in the developing countries, where it can be called a "social calamity".

Organophophates are widely used insecticides world wide specialy in developing countries. The case fatality rate following organophosphate ingestion is 5-20% in Asia. In the United States, there were more than 8000 reported exposures to these agents in 2008, resulting in fewer than 15 deaths. Toxicity generally results from accidental or intentional ingestion of or exposure to, agricultural pesticides. Other potential causes of organophosphate toxicity include ingestion of contaminated fruit, flour, or cooking oil, and wearing contaminated clothing. In one original research article published in Journal of Chitwan Medical College, it was discussed that 88 patients admitted with acute pesticide poisoning and among them organophosphorus is the commonest compound responsible for acute pesticide poisoning.[1] In this study, prevalence of OP poisoning is 47.73% of total poisoning, which is higher than the study conducted in different central and zonal hospital in various parts of country which was (43.0%).Organophosphates are commonly used pesticide in Nepal and responsible for percentage of mortalities contributed by all causes of poison related deaths.

Commonly used organophosphate compounds in Nepal are classified into two group: Diethyl compound and Dimethyl compound. Rate of aging is an important determinant of toxicity and is more rapid(3.7hrs) with dimethyl compound and relatively slower (31hrs) with diethyl compound[12].

DIMETHYL COMPOUND	DIETHYL COMPOUND
• Dichlorvos	• Chlorpyrifos
• Fenthion	• Diazinon
• Malathion	• Parathion-ethyl
• Methamidophos	• Quinalphos

Mechanism of action — Organophosphorus compounds contain carbon and phosphorous acid derivatives. These agents are well absorbed through the skin, lungs, and gastrointestinal tract. They bind to acetylcholinesterase (AChE), also known as red blood cell (RBC) acetylcholinesterase, and render



Theenzyme non-functional. AChE is the enzyme responsible for hydrolysis of acetylcholine to choline and acetic acid, and inhibition leads to an overabundance of acetylcholine at the neuronal synapses and the neuromuscular junction. After some period of time (dependent on the chemical structure of the organophosphorus agent), the acetylcholinesterase-organophosphorus compound undergoes a conformational change, known as "aging," which renders the enzyme **irreversibly** resistant to reactivation by an antidote oxime[12,13,14].

In addition, plasma cholinesterase (also called butylcholinesterase [BuChE] or pseudocholinesterase) and neuropathy target esterase (NTE) are inhibited byorganophosphorus agents; however, the clinical significance of these interactions are less certain[15,16].

Clinical features:

For most agents, oral or respiratory exposures generally result in signs or symptoms within three hours, while symptoms of toxicity from dermal absorption may be delayed up to 12 hours. Lipophilic agents such as dichlofenthion, fenthion, and malathion are associated with delayed onset of symptoms (up to five days) and prolonged illness (greater than 30 days), which may be related to rapid adipose fat uptake and delayed redistribution from the fat stores.

Acute toxicity:

Cholinergic excess — the dominant clinical features of acute cholinergic toxicity include

bradycardia, miosis, lacrimation, salivation, bronchorrhea, bronchospasm, urination, emesis, and diarrhea. Diaphoresis occurs because sweat glands are regulated through sympathetic activation of postganglionic muscarinic receptors. At times, however, mydriasis and tachycardia may be observed, as sympathetic ganglia also contain nicotinic receptors[17,18].

The muscarinic signs can be remembered by use of one of two mnemonics:

- **SLUDGE/BBB** –
  Salivation, **L**acrimation, **U**rination, **D**efecation, **G**astric **E**mesis, **B**ronchorrhea, **B**ronchospasm, **B**radycardia

- **DUMBELS** –
  Defecation, **U**rination, **M**iosis, **B**ronchorrhea/Bronchospasm/Bradycardia, **E**mesis, **L**acrimation, **S**alivation[18]

The nicotinic effects include fasciculations, muscle weakness, and paralysis via acetylcholine stimulation of receptors at the neuromuscular junction. Nicotinic and muscarinic receptors also have been identified in the brain, and may contribute to central respiratory depression, lethargy, seizures, and coma[18].

Cardiac issues — Cardiac arrhythmias, including heart block and QTc prolongation, are occasionally observed in organophosphorus agent poisoning. It is unclear whether these arrhythmias are due to direct toxicity or secondary hypoxemia. Organophosphate compound also causes QTc prolongation by blockade of K+ channel and Na+/Ca+ channel[19].

Respiratory issues — Fatalities from acute organophosphorus agent poisoning generally result from respiratory failure due to a combination of depression of the CNS respiratory center, neuromuscular weakness, excessive respiratory secretions, and bronchoconstriction[20].

Intermediate (neurologic) syndrome — Ten to 40 percent of patients poisoned with organophosphorus develop a distinct neurologic disorder 24 to 96 hours after exposure. This disorder, referred to as the "intermediate syndrome," consists of characteristic neurological findings including neck flexion weakness, decreased deep tendon reflexes, cranial nerve abnormalities, proximal muscle weakness, and respiratory insufficiency.

Risk factors for the development of intermediate syndrome appear to include exposure to a highly fat-soluble organophosphorus agent, and may be related to inadequate doses of oximes. With adequate supportive care, including prolonged mechanical ventilation, most patients have complete resolution of neurologic dysfunction within two to three weeks. Clinical deterioration and improvement appear to correlate with red blood cell (RBC) acetylcholinesterase levels[24-27].

Delayed and long-term neuropathology — Organophosphorus agent induced delayed neuropathy (OPIDN) typically occurs one to three weeks after ingestion of one of a small number of specific organophosphorus agents, including chlorpyrifos. The mechanism may involve inhibition of neuropathy target esterase (NTE), rather than alterations in RBC acetylcholinesterase function.

Affected patients present with transient, painful "stocking-glove" paresthesia followed by a symmetrical motor polyneuropathy characterized by flaccid weakness of the lower extremities, which ascends to involve the upper extremities. Sensory disturbances are usually mild. Delayed neurotoxicity primarily affects distal muscle groups, but in severe neurotoxicity, proximal muscles groups may also be affected. Electromyograms and nerve conduction studies of affected patients reveal decreased firing of motor conduction units. The risk of developing OPIDN is **independent** of the severity of acute cholinergic toxicity. Most cases of mild delayed neurotoxicity improve with time; in severe cases, an upper motor neuron syndrome with spasticity of the lower extremities usually causes permanent disability[25-27].

Additional effects —Several case reports describe acute kidney injury (AKI) requiring renal replacement therapy in the setting of severe organophosphate poisoning[28,29,30]

Severity grading of organophosphate poisoning can be done by peradeniya organophosphorous poisoning scale (POP scale) which has six parameters: pupil size, heart rate, respiratory rate,

fasciculation, level of consciousness and seizure. Score of 0-3 is regarded as mild poisoning, 4-7 is regarded as moderate poisoning and 7-11 is regarded as severe poisoning.

MANAGEMENT: Atropine challenge if diagnosis is in doubt (1 mg IV in adults, 0.01 to 0.02 mg/kg in children). Absence of anticholinergic signs (tachycardia, mydriasis, decreased bowel sounds, dry skin) strongly suggests poisoning with organophosphate or carbamate. Draw blood sample for measurement of RBC acetylcholinesterase activity to confirm diagnosis.

Deliver 100 percent oxygen via facemask; early intubation often required; avoid succinylcholine. **Decontamination** if ingestion within 1 hour give single dose activated charcoal, adult 50 g (1 g/kg in children) unless airway not protected or anothercontraindication. **Atropine** 2 to 5 mg IV/IM/IO bolus (0.05 mg/kg IV in children). Escalate (double) dose every 3-5 minutes until bronchial secretions and wheezing stop. Tachycardia and mydriasis are not contraindications to atropine use. Hundreds of milligrams may be needed over several days in severe poisonings. Inhaled ipratropium 0.5 mg with parenteral atropine may be helpful for bronchospasm; may repeat. **Pralidoxime** (2-PAM) 2 g (25 mg/kg in children) IV over 30 minutes; may repeat after 30 minutes or give continuous infusion if severe Continuous infusion at 8 mg/kg/hour in adults (10 mg/kg/hour in children). If no IV access, give pralidoxime 600 mg IM (15 mg/kg in children <40 kg). Rapidly repeat as needed to total of 1800 mg or 45 mg/kg in children. Pralidoxime is given with atropine. Diazepam 10 mg IV (0.1 to 0.2 mg/kg in children), repeat as necessary if seizures occur. Do not give phenytoin[31-36].

Literature review:

Various studies have been done to find out prognostic value of QT prolongation in organophosphate poisoning and to find out correlation between QT prolongation and ACHE level. They have found that there is definite relation between QT prolongation and severity of organophosphate poisoning. Shahin Shadnia, MD, PhDa, Arash Okazia, Navid Akhlaghia, Ghazal Sasanianb, Mohammad Abdollahib published an article in Journalof Medical Toxicology regarding prognostic value of Long QT interval in Acute and severe Organophosphate poisoning. This was a type of prospective study conducted at Loghman – Hakim Hospital Poison Center (LHHPC). Patients with primary diagnosis of organophosphate poisoning admitted in ICU of this hospital were the subjects of this study. Diagnosis had been established by the history given by relatives, characteristic odor of gastric content, classical signs and symptoms which improves with atropinisation and fall in serum cholinesterase level by more than 25%. Cholinesterase (CE) activity and the QTC interval was determined for each patient using the Bazett formula and considering <440 msec as normal. Comparative outcomes of the study were duration of both hospitalization and mechanical ventilation, serum CE activity on admission and its daily level, total amount of atropine administered, analysis of the QT and QTC intervals in the primary ECG on admission and at the end of hospitalization, and rate of mortality.[2]

The study included 42 patients with a diagnosis of OPP. The mean age of the patients was 32, ranged from 12 to 81 years old. The mortality rate was 37.5%. There was no significant difference between two groups (prolonged and normal QTC intervals) according to gender and age (p = .491 and p = .133, respectively). The CE level for long and normal QTC interval groups was 3.90 _ 0.33 kU/L vs. 4.41 _ 0.23 kU/L, respectively. The mortality rate in the long QTC group was significantly higher than that of the normal QTCgroup (p = .044). Moreover, the average period of hospitalization in patients with prolonged QTC interval was higher than the other group (p = .02). The average atropine required to control the muscarinic signs and symptoms such as salivation, bronchorrhea, and miosis in patients with prolonged QTC interval was 38.60 mg; in patients with normal QTC interval it was 20.02 mg (p = .013).

This indicates that along with the respiratory problems that can cause death in the initial stages of poisoning, cardiac problems can affect the course of illness and the prognosis of patients with OPP. Similar retrospective study was conducted by A. Baydin, D. Aygun, M. Yazici,A. Karatas, T. Deniz, T. Yardan to find out relationship between the blood cholinesterase and QTc interval in the patients with acute organophosphate poisoning(International journal of clinical

practice, June 2007,61,6). This retrospective study consists of 20 patients admitted to the emergency intensive care unit (EICU) of the Ondokuz Mayis University Emergency Department with acute OPP between November2003 and January 2005. Of the 20 patients, 11 were female and nine were male. The ages of the patients ranged from 18 to 73 years, and the mean age was34.3 ± 18.2 years. ECG analysis included rate, rhythm and measurement of QT intervals. The QT intervals were manually measured in every lead possible as previously described, and each QT interval was corrected for heart rate (QTc) by Bazett's Formula (QTc = QT ⁄pRR) (5). QTc-interval prolongation was accepted if it was longer than 440 ms.[3] Thirteen patients were excluded from the study, who had not obtained a blood ChE level on the same day of ECG. The mechanism of intoxication was inattempted suicide for 17 patients (85%) and accidental poisoning for three patients (15%). Route of intake was as follows: 80% by gastrointestinal,15% by inhalation and 5% by intramuscular route.

There were five different types of organophosphate insecticide agents involved. The mental status of the patients on admission was generally good. Thirteen patients (65%) were fully awake (GCS scale 15), three (15%) were drowsy (GCS scale 12–14) and four (20%) were in stupor or coma (GCS scale from 3 to 11). Eight (40%) of the patients needed endotracheal intubation for mechanicalventilation. Two (10%) of the 20 cases with acute poisoning died. The mean duration of staying in EICU was4.4 ± 2.4 days. There was a prolonged QTc interval in 35.4% of the ECGs.There was a negative correlation between QTcinterval and blood AchE measures (r =)0.22; p< 0.05. There were prolonged QTc intervals in 35.4% of the ECGs. There was a negative correlation between QTc interval and blood AChE measures. In following up the patients with acute OPP, QTc interval may be useful when blood ChE levels are low and may provide complementary information concerning the severity of poisoning. Similar retrospective study was conducted by Feng RongChaung (MD), Shyh Woei Jang and colleague regarding QTc prolongation has poor prognosis in patient with organophosphate poisoning. Study was published in AmericanJournalof Emergency Medicine. This study reviewed emergency department electrocardiograms of 223 patients with organophosphate poisoning from January 1982 to June 1994, 97(43.5%) had QTc prolongation and were placed in group A; 126 Patients without QTc prolongation were designated as group B. compared with group B, group A patients had a higher mortality (19.6% v 4.8%, p<.001) and a higher incidence of respiratory failure(56.7% v 20.6%, p<.001). serum cholinesterase levels were determined in the 223 patients: 92(41.3%) were classified as severe poisoning, 32(14.3%) as moderate, 41(18.1%) as mild, and 58(25.7%) as very mild. The severe group had a high incidence of QTc prolongation (p<.001), a high incidence of respiratory failure (p<0.001), and a higher mortality rate (p<0.001) than the other groups. Of the QTc prolongation patients, 59.8%(55/92) had a high incidence of respiratory failure (78.2% v 35.1%, p<0.001) and a higher mortality rate (29.1% V 8.1%, P<0.05) compared with 40.2%(37/92) of the patients without QTc prolongation in the severe group. In conclusion, a complete electrocardiogram at the emergency department is important and of prognostic value.[4] Similar prospective observational study was published in Academic EmergencyMedicine, by Stefek Grmec, MD, PhD, Stefan Mally, MD, Petra Klemen, MD regarding Glasgow Coma Scale Score and QTc Interval in the Prognosis of Organophosphate Poisoning. Aim of this study was to assess the applicability of the Glasgow Coma Scale (GCS) score and the Q-T interval corrected for heart rate (QTc interval) in predicting outcome and complications in patients with organophosphate (OP) poisoning. Study Design was a prospective observational study undertaken over a nine-year period from February 1993 to May 2002. The study received approval from the Ethical Review Board of the Ministry of Health of Slovenia. The study was performed in the out-of-hospital setting, and included65 consecutive patients (39 male and 26 female) withOP poisoning.

Fifty-nine patients (90.8%) with OP poisoning had attempted suicide, four (6.1%) were poisoned by unintentional ingestion, and two (3.1%) were exposed to OPs in their occupations. Fifty-nine patients (90.8%) were from rural areas. Twenty-four patients (36.9%) presented in a coma. The estimated mean time between exposure and ICU admission was 6.3 hours (range, 1–28 hours). Muscarinic features of OP poisoning (SLUDGE [salivation, lacrimation, urination, diarrhea,

gastrointestinal upset, emesis] and DUMBELS [diaphoresis, urination, miosis, bradycardia, bronchospasm, bronchorrhea, emesis, lacrimation excess, salivation excess]) were predominant clinical manifestations (n = 53, 81.5%). Central nervous system disturbances (anxiety, confusion, tremor, ataxia, seizures, dysarthria, and coma) were present in 45patients (69.2%), and 14 patients (21.5%) manifested nicotinic signs and symptoms (muscle fasciculations, muscle cramping, weakness, hypertension, tachycardia, pupillary dilatation, and pallor). Endotracheal intubation was performed in 52.3% (n = 34) of patients due to bronchorrhea (n = 29, 85.3%), laryngospasm and bronchospasm (n = 16, 47.1%), altered level of consciousness (n = 23, 67.6%), and hemodynamic instability (n = 10, 29.4%). The median serum cholinesterase level was 295 IU/L (range, 60–8,020 IU/L). The time course between initial recognition of prognostic variables (consecutive intubation in the field) and their endpoint (recovery in ICU) or the mean 6 SD ventilation duration was 182.5 6 127.2 hours (range,23–598 hours). Patients with RF were significantly older and had worse outcomes than those in the group without complications.[5]

There was a significant difference in ETCO2, SaO2, QTc interval,GCS score, and Acute Physiology and Chronic Health Evaluation II (APACHE II) values, and in intubation and mortality rates between groups (p \ 0.05). The mean serum cholinesterase levels were not significantly different between groups (p = 0.38). Prolongation of the QTc interval was observed in 26 of 31 or83.8% (95% CI = 78.2% to 90.4%) in the group with RFand in 16 of 34 or 47.1% (95% CI = 42.9% to 52.1%) in the group without complications (p \ 0.05). Furthermore, interval prolongation was observed in 29 of34 or 85.3% (95% CI = 78.6% to 93.1%) of those patients requiring intubation and in 13 of 31 or41.9% (95% CI = 35.6% to 48.1%) of patients who did not require intubation. A GCS score of 8 was observed in 18 of 23 or 78.3% (95% CI = 71.6% to 85.1%) of those patients requiring intubation in the group with RFand a GCS score of 8 was observed in 5 of 11 or 45.4%(95% CI = 33.8% to 57.2%) of those patients requiring intubation in the group without RF. Comparison between the GCS score and QTc interval showed no significant difference in predicting RF and in-hospital mortality. Results suggest that emergency care providers may use GCS scores and QTc intervals to detect patients with OP poisoning who will potentially suffer RF, and to assess the patients' final prognoses. Another study was published by Shou-Hsuan Liu, Ja-Liang Lin, Cheng-Hao Weng, Huang-Yu Yang, Ching-Wei Hsu, Kuan-Hsing Chen, Wen-Hung Huang, Tzung-Hai Yen in PLoS ONE regarding Heart Rate-Corrected QT Interval Helps Predict Mortality after Intentional Organophosphate Poisoning. They analyzed the records of 118 patients who were referred to Chang Gung Memorial Hospital for management of organophosphate poisoning between 2000 and 2011. Patients were grouped according to their initial QTc interval, i.e., normal (<0.44 s) or prolonged (>0.44 s). Demographic, clinical, laboratory, and mortality data were obtained for analysis.[6]

The incidence of hypotension in patients with prolonged QTc intervals was higher than that in the patients with normal QTc intervals (P = 0.019). By the end of the study, 18 of 118 (15.2%) patients had died, including 3 of 75 (4.0%) patients with normal QTc intervals and 15 of 43 (34.9%) patients with prolonged QTc intervals. Using multivariate-Cox-regressionanalysis, we found that hypotension (OR = 10.930, 95% CI = 2.961–40.345, P = 0.000), respiratory failure (OR = 4.867, 95% CI = 1.062–22.301, P = 0.042), coma (OR = 3.482, 95% CI = 1.184–10.238, P = 0.023), and QTc prolongation(OR = 7.459, 95% CI = 2.053–27.099, P = 0.002) were significant risk factors for mortality. Furthermore, it was revealed that non-survivors not only had longer QTc interval (503.00641.56 versus 432.71651.21 ms, P = 0.002), but also suffered higher incidences of hypotension (83.3 versus 12.0%, P = 0.000), shortness of breath (64 versus 94.4%, P = 0.010), bronchorrhea (55 versus 94.4%, P = 0.002), bronchospasm (50.0 versus 94.4%, P = 0.000), respiratory failure (94.4 versus 43.0%, P = 0.000) and coma (66.7 versus 11.0%, P = 0.000) than survivors. Finally, Kaplan-Meier analysis demonstrated that cumulative mortality was higher among patients with prolonged QTc intervals than among those with normal QTc intervals (Log-rank test, Chi-square test = 20.36, P,0.001). In summary, they concluded that QTc interval helps predict mortality after intentional organophosphate poisoning.

Another similar study regarding Long QT and ST-T change associated with organophosphate exposure by aerial spray published by Kumiko Taira, Yoshiko Aoyamab, Miwako Kawamata in Environmental Toxicology and Pharmacology. The relation between the electrocardiographic manifestation and the subjective symptoms accompanying organophosphate pesticide exposure caused by aerial spray was investigated. The study included 39 patients with a diagnosis of organophosphate poisoning, who visited A-clinic within 24 h of exposure to aerial spray of organophosphate pesticide in Gumma Prefecture, from July 2001 to September 2001. Ages ranged from 3 to 82 years. Thirty-five patients were female. Three were diagnosed as severe, 11 moderate, and 25 mild, judged from the score of subjective symptoms. Electrocardiographic abnormalities were bradycardia (<50) 2; prolonged PQ interval 4; prolonged QTc interval (>430 ms) 22; nonspecific ST-T change 35; supraventricular arrhythmia 13; and ventricular premature complex with R on T 1. Prolonged QTc interval developed in 2–3 severe cases, 4–11 moderate cases, and 16–25 mild cases. QT prolongation, ST-T change and arrhythmia were detected for some patients exposed to organophosphate by aerial spray.[7]

Another study on electrocardiographic findings in acute organophosphate poisoning was conducted by Yusuf Yurumez, MD, Yucel Yavuz, MD, Hayrettin Saglam, MD, Polat Durukan, MD, Seda Ozkan, MD, Okhan Akdur, MD, and Murat Yucel, MD and published in The Journal of Emergency Medicine. Over a period of 3 years (January 2002 to December 2004), 90 patients with OP poisoning were admitted by them to the ED of Erciyes University Medical School Hospital in Kayseri, Turkey. Eighty-five cases of poisoning were included and they excluded 5 cases due to a past history significant for cardiac disease. They admitted patients to the intensive care unit (ICU) directly from the ED. The diagnosis was based on the history of OP compound exposure and corresponding clinical features.[8]

Seventy-three (85.9%) patients had ingested the OP compound. The patients presented to us as early as 30 min to as long as 22 h after contact with the poison; 34.1% of the patients presented to us within 2 h after exposure, and the mean time interval was 4 h, 13 min. The most commonly involved OP compound was dichlorvos, which was implicated in 15 (17.6%) patients. Cardiac manifestations and ECG changes that were recorded before the administration of atropine. The mean QTc interval was 0.4350(min: 0.35, max: 0.59). There was no significant difference in the mean QTc interval between males (0.445s) and females (0.428s) ($p < 0.05$). Forty-seven patients (55.5%; 23 males and 24 females) had a prolonged QTc interval. Prolongation of the QTc interval was the most common ECG abnormality, followed by sinus tachycardia (31.8%). Twelve patients (14.1%) had extremely prolonged QTc intervals (0.50 s).

Nonspecific ST segment elevation (0.2 mV above the isoelectric line) and low amplitude T-wave changes were seen in 15 cases (17.6%). Six of 15 cases with ST-T changes complained of chest pain, as did a case without-T change. First-degree heart block (PR interval = 0.20 s) occurred in one case (1.2%). No other conduction defect was observed. Ventricular tachycardia was not seen in our cohort. Hypertension (systolic pressure _160 mm Hg or diastolic pressure 95 mm Hg) was observed in three cases (3.6%), and hypotension (systolic atrial pressure 90 mm Hg) occurred in two cases (2.4%). The cardiovascular and electrocardiographic abnormalities all returned to normal before the patients were discharged. Thirty-four patients (40%) were discharged from the ED; 51 patients (60%) were admitted to the ICU. In the present study, atropine and pralidoxime treatment were given to 70.6% and 54.1% of the patients, respectively. Two patients (2.4%) died despite appropriate treatment. One of them was a 69-year-old man with QTc interval of 0.44 s, and the other was a 24-year old woman with QTc interval of 0.40 s.In conclusion, patients with OP poisoning might revealECG abnormalities such as QTc interval prolongation or non-specific ST-T changes.

Another study was conducted by Gouda H.S, Rohith K, P Sasanka, D.R Mahadeshwara Prasad, K.H Manjula Baion Pre-Interventional Cardiac and ECG Changes in Acute Organophosphate Poisoning Cases Admitted to a Tertiary Hospital in India and published in International Journal of Medical Toxicology and Forensic Medicine. They studied clinical records of acute organophosphate poisoning patients of age less than 50 years admitted to KLE's Dr. Prabhakar Kore Hospital,

Belgaum, Karnataka, from 01-01-2010 to 31-12-2010. They excluded Cases of organophosphate poisonings referred from other hospitals, poisoning with multiple agents, patients with history of previous cardiac diseases and coexisting medical conditions. Poisoning Severity Score was calculated as per International Programme on Chemical Safety and patients were grouped into 3 grades.[9]

In this study, 50 cases of acute organophosphate poisoning (male - 32; female - 18) were analyzed. Sinus tachycardia was present in 45 patients (90%), hypertension in 13 (26%) and hypotension in 12 (24%). Prolonged corrected QT interval was observed in 14 patients (28%), elevated ST segment in 2 (4%), inverted T wave in 13 (26%) and conduction defects in 1 (2%). Among 14 patients with prolonged corrected QT interval, 12 were in grade III and 2 in grade II severity; and, among 13 patients who had inverted T wave, 2 were in grade I, 4 in grade II and 7 in grade III severity. Acidosis, as assessed by blood pH and HCO3, was observed in 22 patients (44%).

They concluded that Fatal cardiac complications do occur in acute organophosphate poisoning, which are overlooked at times as the most common complications expected are respiratory complications. Higher incidence of ECG changes in Grade III cases suggests that if the cardiac complications develop, the patient should be immediately transferred to an intensive cardiac care unit

Similar analytical study of ECG changes of organophosphoruspoisoning was done by Vijaya Kumar G, Prabhakar Rao R and Srikanth Pand published in International Journal of Recent Scientific Research. Their aim was to study importance of electrocardiographic changes in Organophosphate poisoning and to analyze their relationship as predictors of final outcome.

All the cases with alleged organophosphorus poisoning are taken for study. Patient with history of Hypertension, coronary artery disease and drugs use causing ECG abnormalities were excluded from study.ECG obtained at time of admission before giving atropine and PAM, during hospital stay and at time of discharge. The result of outcome of patients was interpreted and correlated with ECG abnormalities.

In this study the peak incidence seen in age of 21-30 years in both sexes. Sex incidence: 44cases male and 36 cases of female that male: female=1.2:1. They found a polymorphic ventricular tachycardia of the torsade de pointes type attributed to a prolongation of the Q-Tc interval in majority of patients (28%). Arrhythmias were detected in 54%. theyobserved 36% QTc interval prolongation and was the most commonECG abnormality seen in 28% of their patients.

HYPOTHESIS:

QTc prolongation has prognostic value in organophosphate poisoning.

Objectives

General objectives

To find out QTc interval in diagnosed case of organophosphate poisoning.

Specific objectives:

1. To calculate corrected QT interval (QTc) in diagnosed case of organophosphate poisoning by Bazett's formula (QTc = QT/√RR).
2. To find out ACHE level in patient with organophosphate poisoning.
3. To calculate POP score in patient with organophosphate poisoning.
4. To observe and find out total dose of atropine to achieve full atropinisation.
5. To calculate GCS score at admission.
6. To observe and find out total day of admission in Hospital.
7. To find out percentage of patient developing organ dysfunction.
8. To find out rate of ICU admission of OP poisoning with QTc prolongation.

Materials and methods:

Type of Study

This study is a cross sectional observational hospital-basedstudy with data collected at the time of admission and then once patient is stable and ready for discharge from the hospital.

Place of Study

Patients were recruited for study subject to providing informed consent who are admitted in Bir Hospital, NAMS.

Study Period

Patient were recruited for the study for a period of

12 months from 1st of March 2018 to 1st of February 2019.

Sample Size

Formula for calculation of sample size for estimation of proportion

$$n = \frac{z^2 p(1-p)}{d^2} \text{ for very large population}$$

- here, proportion (*p)* = 0.5785 which is the prevalence of QTc in organophosphate poisoning[40]
- Confidence level = 95% (Z=1.645)
- Precision (d) = 0.10 which is the maximum tolerable error

1.645^2x0.5785(1-0.5785)/0.10^2= 65.98

Hence sample size needed for the study is 66patients

Sampling Technique:

Non probability convenient sampling was applied. Individual admitted to the hospital with organophosphate poisoning meeting the inclusion criteria set are recruited for the study.

Inclusion Criteria

Patients must meet all criteria

1. Male or female subjects, aged below 75 years
2. Patient with definite history suggestive of organophosphate poisoning.
3. Patient with ACHE level below normal.
4. Patient with alleged h/o organophosphate compound ingestion presented within 24 hours.
5. Patient or relative who gave written informed consent.
6. Patient's current admission primarily for organophosphate intoxication.

Exclusion Criteria:

None of the following criteria should be met

1. Patient age more than 75-year-old.
2. Patient having known h/o acquired and congenital long QT syndrome.
3. Patient under treatment with Antiarrhythmic drugs, Certain non-sedating antihistamines (eg, terfenadine and astemizole), Certain antimicrobials (eg, macrolide and fluoroquinolone antibiotics, some antifungal and antiviral drugs, etc), Certain psychotropic medications, Certain gastric motility agents (eg, cisapride) which prolong QT.
4. Patient with h/o intravenous drug use.
5. Patient with h/o alcohol dependence with CAGE = 3 or 4
6. Patient having previous h/o organophosphate intoxication.

Methodology:

This study is a hospital based cross-sectional observational study conducted at Bir-Hospital from 1st of March 2018 to 1st of February 2019. Altogether 66 patients below 75 years of age non-alcoholic without known co-morbidities admitted in general ward and ICU full filled inclusion criteria. They were enrolled in this study after taking informed consent. They were thoroughly examined and investigated. Specially ECG, CBC, RFT, LFT, PT/INR, ABG, Chest X-Ray, Serum ACHE done at admission and during course of admission as per requirement. Personal and demographic parameters were recorded. Details of OP compound, amount ingested, duration of ingestion before presentation, total dose of atropinization, place of admission, complications developed during admission and duration of admission were recorded. Patients were grouped into age class intervals, severity of poisoning done on the basis of ACHE level and POP score at admission. QTc calculated by Bazzet's formula, grouped into normal and prolonged categories. Statistical analysis was done by SPSS 20 and statistically significant tests were applied depending on type of variable as per need of this study.

Peradeniya organophosphorous poisoning scale (pop scale):

Parameter	criteria	score
Pupil size	≥2mm	0
	≤2mm	1
	Pinpoint	2
Heart rate	≥60	0
	41-60	1
	≤40	2
Respiratory rate	≤20	0
	≥20	1

	≥20 with central cyanosis	2
Fasciculation	None	0
	Present, generalized/continuous	1
	Both generalized and continuous	2
Level of consciousness	Conscious and rationale	0
	Impaired response to verbal command	1
	No response to verbal command	2
Seizure	Absent	0
	Present	1
GRADING OF SEVERITY		
Mild poisoning = 0-3, moderate poisoning = 4-7, severe poisoning = 8-11		

Data collection:

Recording done during the study are as follows:

1. Patients biodata
2. Patients underlying medical co-morbidities
3. Any history of myocardial infarction or heart failure
4. Duration since the diagnosis of organophosphate intoxication.
5. Patient's current medications.
6. History of previous organophosphate intoxication.
7. Measurement of oxygen saturation via finger pulse oxymeter will be done.
8. Findings of ACHE reports done at admission
9. Patient's ECG findings which are routinely done in hospital specially QT interval and QTc calculated by Bazett formula.
10. POP score at admission.
11. GCS score at admission.
12. Total dose of ATROPIN used to achieve full atropinisation.
13. Admitted in ICU or General ward.
14. If admitted in ICU, then patient is under mechanical ventilation or not.
15. RFT, LFT
16. Has h/o aspiration pneumonia during admission or not.
17. All variable will be collected and listed in Performa and data will be analyzed as per Performa.

Instruments and Personnel required:

Patient's biodata and medical history were taken and Pulse oximeterwas used to measure oxygen saturation. ECG is done routinely hence reports were collected. Patients are routinely advised AChE level hence data were collected from lab. RFT and LFT are done routinely so reports were collected.

Statistical analysis:

Data were analysed using IBM SPSS Statistics 20. Descriptive data were summarized using standard techniques and reported as percentage with 95% confidence interval. Continuous data are presented as mean +/- SD and categorical data are as absolute numbers and percentages. The student's t-test and chi-square test were used for comparison of continuous and categorical variables between groups respectively. Fisher's exact test is used for analysing difference between two groups when there were cells < 5. Correlation between continuous variables was assessed using Pearson's correlation. A linear regression was used to assess association between QTc interval and primary predictors. The predictive value of QTc interval and clinical outcome was assessed by logistic regression. The mean difference in variables was evaluated by the Analysis of variance (ANOVA) test. A level of significance was set at the 0.05 level.

Ethical consideration:

Approval from Institutional Review Board (IRB) of NAMS was obtained before the study. A written informed consent was obtained from all participants. A document was obtained from every patient showing they have understood the consent and their approval in participating in the study. Participants were explained regarding the study procedure, significance and its importance to the community and for further research. Patients were explained in a language patient understand well. Every querywasclarified before patient party signed the consent. Participants were ensured confidentiality and explained regarding possibility of withdrawal of consent at any time during the study. Patients had not beard any additional cost due to the study as information obtained for the

study is from their routine investigations. I hadobtained information from patients with full disclosure regarding the study.

Observation and results:

All together 66 patients were enrolled in this study out of which 44(66.7%) were female and 22(33.3%) were male.

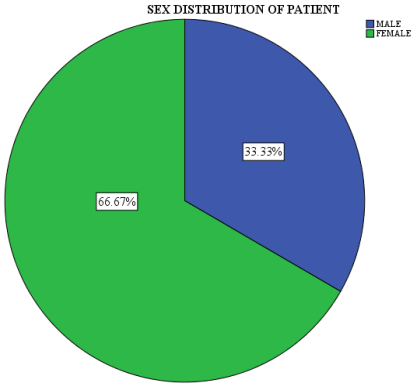


Figure 1: pie chart showing sex distribution.

Maximum age of participant was 73 year and minimum age was 14 year with mean of 33.03 and SD of 12.921. Minimum weight of participant was 40 kg with BMI of 21.0 and maximum weight was 78kg with BMI of 32.40. Mean weight of participant was 52.85kg with SD of 8.192 and mean BMI was 23.7152 with SD of 1.491.Most of them were married (81.8%). For simplicity of comparison and easy of calculation, age of participant was divided into class interval and frequency was calculated for each class interval.

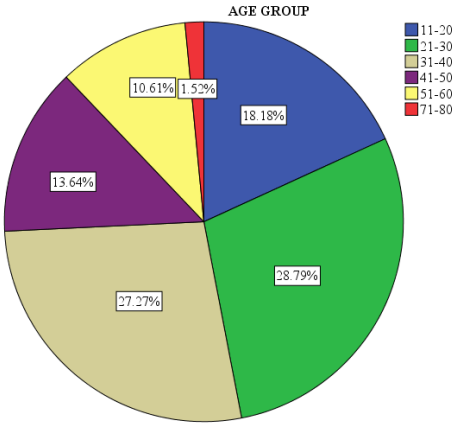


Figure 2: total percentage of participant within specified class interval.

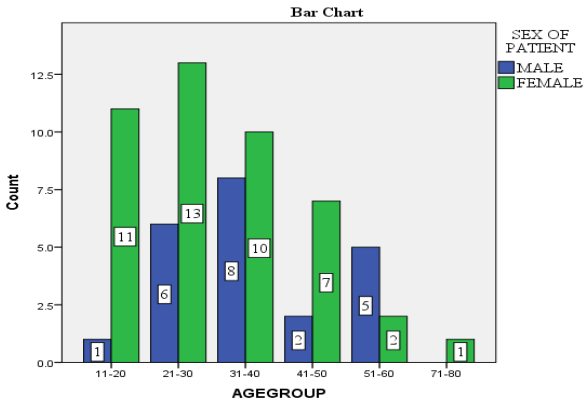


Figure 3: Bar chart showing sex distribution across all class intervals

During this study, It was found that there were 6 types of organophosphate compounds used by patients and 50% were found to be using chlorpyrifos (50%) + cypermethrin (5%). Overall 50% were using diethyl compounds and 50% dimethyl compounds.

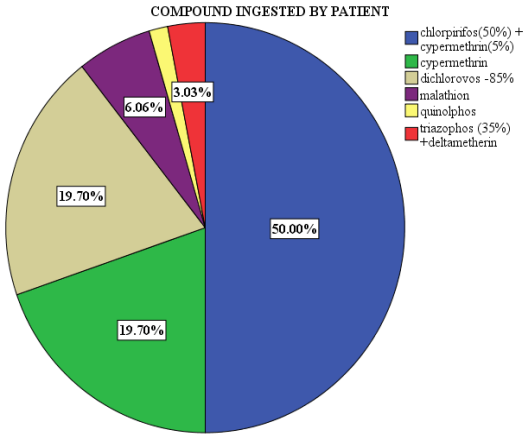


Figure 4: pie chart showing organophosphate compounds used by patient and their percentage.

There is no significant difference between dimethyl and diethyl compounds while comparing their effect on Renal Function Test, Liver Function Test and requirement of mechanical ventilation but there is significant difference between them in regard to vasopressors requirement and severity of poisoning. During this study, 18.2% of cases were found to have severe poisoning (ACHE LEVEL <700 U/L), among which 16.7% were contributed by diethyl compounds and only 1.5% were contributed by dimethyl compounds (Fisher exact test, p = 0.005). Requirement of vasopressors among diethyl compound consumer were significantly higher (21.2%) while comparing with dimethyl group (7.6%) (Fisher exact test, p=0.028).

Complications were seen significantly higher in diethyl group (16.6% vs 4.5%) (Fisher exact test, p = 0.035).

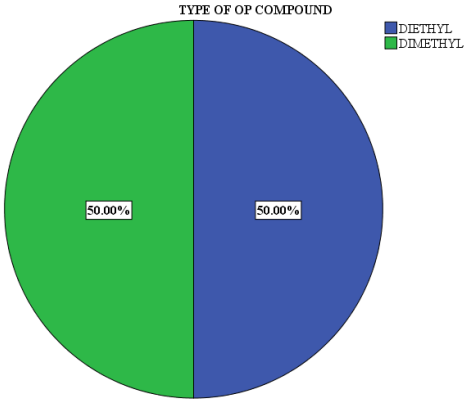


Figure 5: pie chart showing types of organophosphate compounds used by patients and their percentage.

While comparing among organophosphate compounds ingested by patients, chlorpyrifos (50%) + cypermethrin (5%) group had maximum number of patients developing severe poisoning.

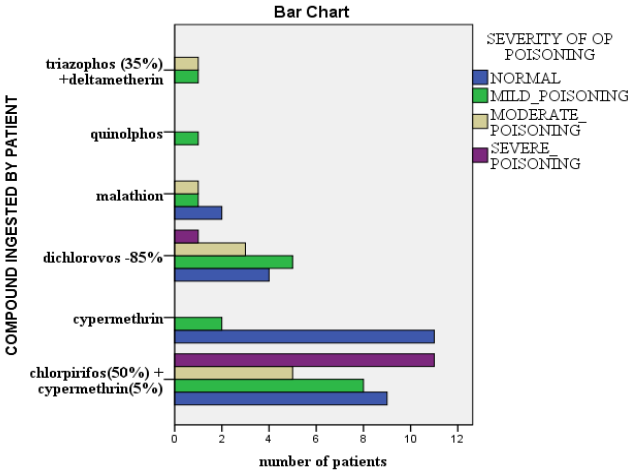


Figure 6: Bar chart showing number of patients with severe poisoning among all individual compounds ingested by them [mild poisoning (ACHE = 0-700 U/L), moderate poisoning (ACHE = 701-1400) & severe poisoning (ACHE = 1401-3500)]

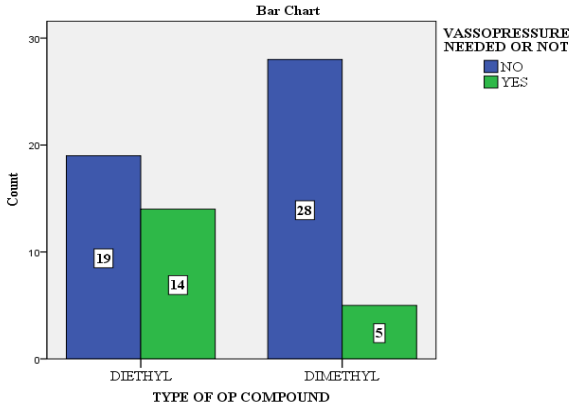


Figure 7: Bar Chart showing number of patients requiring vassopressure support in diethyl and dimethyl group.

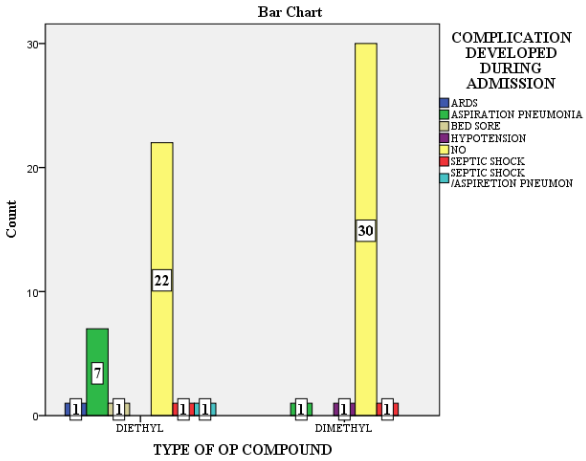


Figure 8: Bar chart showing complications developed and their frequencies among diethyl and dimethyl group.

Maximum and minimum QT recorded were 390.90 and 240ms respectively with respective mean and SD of 340.61 and 32.56. Similarly, maximum and minimum QTc calculated were 650.80 and 370.50ms respectively with respective mean and SD of 427.73 and 42.53. Distribution of data among calculated QTc was normal. When considering overall normal QTc among male and female be less than 440ms, then 44(66.7%) patient had normal QTc and 22(33.3%) patient had prolonged QTc. Among prolonged QTc group, 7(31.8%) were male and 15(68.2%) were female. Overall 10.6% of male and 22.7% of female had prolonged QTc. But while considering separate normal value in male (less than 430ms) and female (less than 450ms), 10(15.2%) male and 11(16.7%) female had prolonged QTc interval with total patients with prolonged QTc of 31.9%.

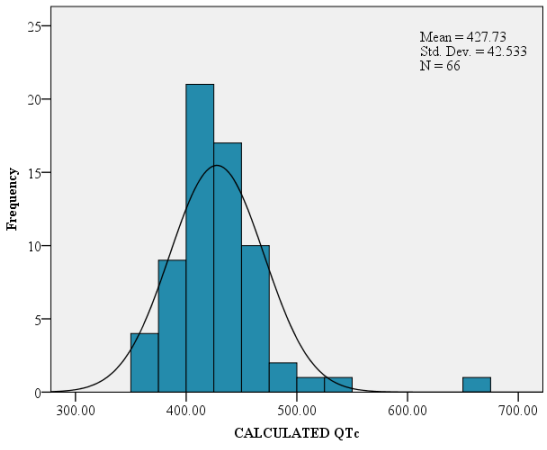


Figure 9: histogram showing normal distribution and skewness of calculated QTc.

Figure 10: Bar chart showing sex distribution of normal QTc and prolonged QTc considering normal QTc be less than 440ms.

I had compared the calculated QTc among patients with normal and deranged LFT by performing independent sample t-test, which showed that mean QTc value is significantly higher (M = 490.33, SD = 82.44) among patients with deranged LFT than the mean QTc value (M = 421.47, SD = 31.28) of patients with normal LFT (t(64) = -4.25, p = 0.001) but there is no statistically significant difference in mean QTc when comparing among patients with normal and deranged RFT(t(64) = -1.26, p = 0.211). There is no statistically significant difference in mean QTc value when comparing the same among male and female (t (64) = 0.627, p = 0.533). When comparing between diethyl and dimethyl group, mean QTc (M = 441.92, SD = 52.35) is significantly higher among diethyl group than the mean QTc (M = 413.55, SD = 22.78) among dimethyl group (t (64) = 2.85, p = 0.006).

I wanted to see whether patients with prolong QTc have more frequent requirement of mechanical ventilation or not. For that I performed Fisher exact test which showed that there is no significant association between QTc prolongation and requirement of mechanical ventilation (Fisher exact test, p = 1.00). But there is statistically significant association between QTc prolongation and vassopressure requirement (X^2 (1) = 22.98, p <0.001).

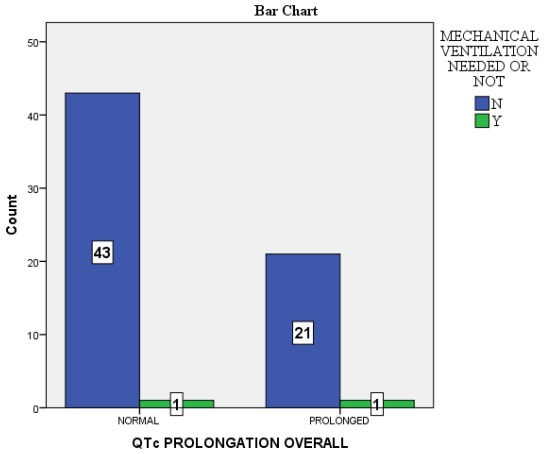


Figure 11: Bar chart showing number of patients requiring mechanical ventilation among normal QTc and prolonged QTc group.

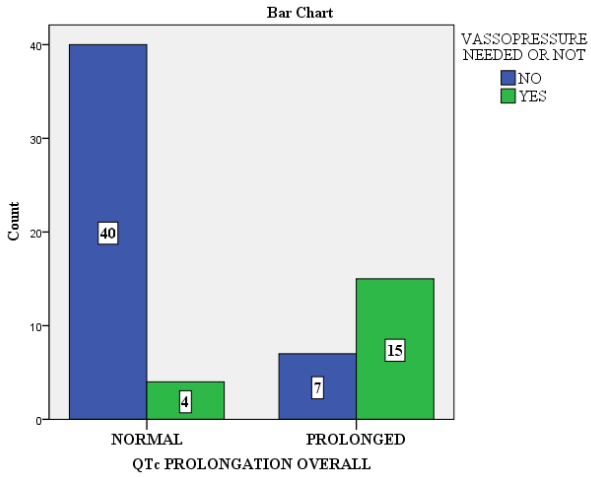


Figure 12: Bar chart showing frequency of patients needing vassopressure support among normal QTc and prolonged QTc group.

To measure the strength of association between amount of organophosphate compound ingested and calculated QTc, I used spearman's rho non parametric correlations which showed a positive correlation between amount of OP compound ingested and QTc level at rs(66) = 0.466, p < 0.01. There was positive correlation between total dose of atropinization and QTc level as well [rs(66) = 0.623, p <0.01].

A simple linear regression was calculated to predict POP score based on calculated QTc values, b = 0.402, t (64) = -2.20, p = 0.032. A significant regression equation was found [f (1,64) = 12.354, p = 0.001] with an R^2 of 0.162. A significant regression was also found when it was calculated to predict GCS Score based on calculated QTc; b = -0.25, t (64) = 17.55, p<0.001

[f (1,64) = 4.155, p = 0.046 with an R^2 of 0.061].

While comparing with normal QTc group, prolonged QTc group had significantly higher rate of complication developed during course of treatment; ARDS (1.5% VS 0%), Aspiration Pneumonia (7.6% vs 4.5%), Bed Sore (1.5% vs 0%), septic shock (3% vs 0%) [Fisher's exact test, p<0.001].

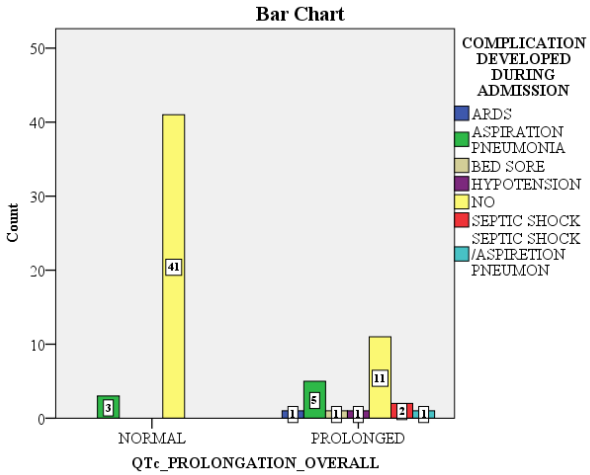


Figure 13: Bar chart showing complications and their frequencies developed during course of treatment among normal QTc group and prolonged QTc group.

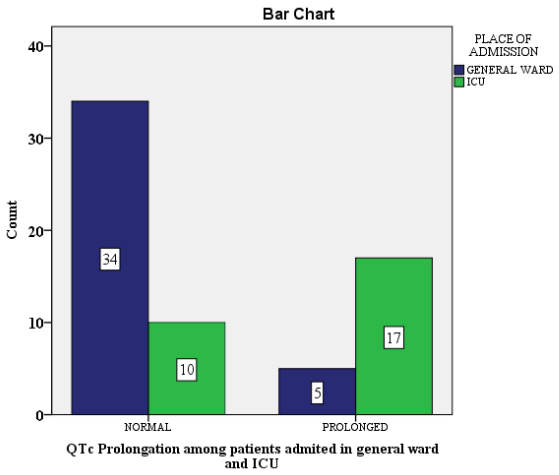


Figure 14: Bar chart showing frequencies of admission in general ward and ICU among normal QTc and prolonged QTc group.

Descriptive study of baseline characteristics across normal and prolonged QTc interval

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
AGE OF PATIENT	**NORMAL QTc**	44	30.91	11.798	1.779	27.32	34.50	14	60
	PROLONGED QTc	22	37.27	14.263	3.041	30.95	43.60	15	73
	Total	66	33.03	12.921	1.590	29.85	36.21	14	73
AMOUNT INGESTED IN ml	**NORMAL QTc**	44	22.16	21.114	3.183	15.74	28.58	5	100
	PROLONGED QTc	22	48.18	29.783	6.350	34.98	61.39	10	100
	Total	66	30.83	27.098	3.336	24.17	37.49	5	100
TOTAL DOSE OF ATROPINE REQUIRED TO ACHIEVE ATROPINIZATION IN ML	**NORMAL QTc**	44	29.39	46.849	7.063	15.14	43.63	5	240
	PROLONGED QTc	22	61.68	31.608	6.739	47.67	75.70	16	125
	Total	66	40.15	44.834	5.519	29.13	51.17	5	240
POP SCORE AT ADMISSION	**NORMAL QTc**	44	1.61	1.061	.160	1.29	1.94	0	4
	PROLONGED QTc	22	3.14	1.490	.318	2.48	3.80	0	6
	Total	66	2.12	1.409	.173	1.77	2.47	0	6
SBP AT PRESENTATION	**NORMAL QTc**	44	111.30	12.882	1.942	107.38	115.21	80	130
	PROLONGED QTc	22	102.91	16.489	3.516	95.60	110.22	90	150
	Total	66	108.50	14.611	1.799	104.91	112.09	80	150
GCS	**NORMAL QTc**	44	15.00	.000	.000	15.00	15.00	15	15
	PROLONGED QTc	22	14.59	1.333	.284	14.00	15.18	10	15
	Total	66	14.86	.782	.096	14.67	15.06	10	15
BODY MASS INDEX	**NORMAL QTc**	44	23.3750	.88374	.13323	23.1063	23.6437	21.60	25.60

	PROLONGED QTc	22	24.3955	2.13329	.45482	23.4496	25.3413	21.00	32.40
	Total	66	23.7152	1.49061	.18348	23.3487	24.0816	21.00	32.40
SERUM ACETYLCHOLINESTERASE AT TIME OF ADMISSION(U/L)	**NORMAL QTc**	44	3710.1364	2180.13246	328.66734	3047.3155	4372.9572	500.00	12500.00
	PROLONGED QTc	22	1883.7727	2253.47247	480.44195	884.6390	2882.9064	300.00	8500.00
	Total	66	3101.3485	2353.20119	289.65904	2522.8594	3679.8375	300.00	12500.00
TOTAL WBC COUNT DURING ADMISSION	**NORMAL QTc**	44	7020.45	2973.650	448.295	6116.38	7924.53	5000	24000
	PROLONGED QTc	22	7627.27	4036.640	860.614	5837.53	9417.02	1600	18000
	Total	66	7222.73	3346.217	411.891	6400.12	8045.33	1600	24000

Overall 18.2% had severe poisoning (ACHE = 0-700 U/L), 15.2% had moderate poisoning (701-1400 U/L) and 27.3% had mild poisoning (1401-3500 U/L). Mean QTc level in mild, moderate and severe poisoning group are 430.08 ms, 446.32 ms and 446.09 ms respectively. Although mean QTc of group with lower ACHE level is comparatively higher but there is no significant difference in mean QTc level when comparing between groups and within group [F (2,37) = 0.550, p = 0.58]. when comparing QTc among those admitted in general ward and those admitted in ICU, mean and SD for those admitted in ICU (451.81 & 51.20) is significantly higher than those admitted in general ward (411.07 &24.58) [t (64) = -4.31, p <0.001].

ANOVA

		Sum of Squares	**df**	**Mean Square**	**F**	**Sig.**
ATROPINIZATION DOSE RANGE	Between Groups	53.455	1	53.455	32.624	.000
	Within Groups	104.864	64	1.638		
	Total	158.318	65			
TOTAL ADMISSION DURATION GROUP	Between Groups	3.030	1	3.030	7.459	.008
	Within Groups	26.000	64	.406		
	Total	29.030	65			
POP SCORE SEVERITY GROUP	Between Groups	1.939	1	1.939	17.174	.000
	Within Groups	7.227	64	.113		
	Total	9.167	65			
ACHE SEVERITY GROUP	Between Groups	6.178	1	6.178	10.241	.003
	Within Groups	22.922	38	.603		
	Total	29.100	39			
GCS SEVERITY GROUP	Between Groups	.121	1	.121	4.267	.043
	Within Groups	1.818	64	.028		
	Total	1.939	65			
AGE CLASS INTERVAL	Between Groups	5.939	1	5.939	3.450	.068
	Within Groups	110.182	64	1.722		
	Total	116.121	65			
RENAL FUNCTION TEST	Between Groups	.008	1	.008	.251	.618
	Within Groups	1.932	64	.030		
	Total	1.939	65			

LIVER FUNCTION TEST	Between Groups	.614	1	.614	8.113	.006
	Within Groups	4.841	64	.076		
	Total	5.455	65			

CHI-SQUARE & ANOVA ANALYSIS RESULT ACROSS DIFFERENT GROUPS[a]					
			Score	df	**Sig.**
Step 0	Variables	DURATION OF ADMISSION GROUP	6.889	1	**.008**
		VENTILATOR SUPPORT (1)	.258	1	**.612**
		VASSOPRESSURE SUPPORT (1)	24.981	1	**.000**
		LFT (1)	7.425	1	**.006**
		RFT (1)	.258	1	**.612**
		AGE	3.612	1	**.068**
		AMOUNT INGESTED	13.734	1	**.000**
		DOSE OF ATROPINIZATION	7.727	1	**.000**
		POP SCORE	17.395	1	**.000**
		GCS	4.073	1	**.044**
		ACETYLCHOLINESTERASE LEVEL	8.971	1	**.003**
		BMI	6.979	1	**.008**
a. Residual Chi-Squares are not computed because of redundancies.					

Discussion:

Altogether 66 patients were enrolled in this study off which 44(66.7%) were female and 22(33.3%) were male. 50% of them had used diethyl and 50% had used dimethyl compound for poisoning. Among both group, 50% had used chlorpyrifos (50%) + cypermethrin (5%). Severe poisoning is significantly higher in diethyl group (16.7% vs 1.5%) than in dimethyl group at p = 0.005. vasopressor requirement (21.2% vs 7.6%) at p = 0.028 and complications developed (16.6% vs 4.5%) at p = 0.035 were significantly higher among diethyl group.

When considering 440ms as cut-off value for QTc, 22(33.3%) had prolonged QTc. Mean QTc(464.85ms) among patient with moderate poisoning (POP score severity) was significantly higher than those with mild poisoning [p = 0.001]. Mean QTc for patients with deranged LFT was significantly higher than those with normal LFT at p = 0.001. There was statistically significant association between QTc prolongation and vasopressor requirement [(X2(1) = 22.98, P<0.001]. One death was recorded who was a 40-year-old female from whose ACHE level was 600U/L, QTc recorded was 470.90ms. She was admitted in ICU for vasopressor and ventilator support. Mean QTc for patients admitted in ICU was significantly higher than those admitted in general ward [p<0.001]. Prolonged QTc value predicted higher POP score [p = 0.001] with an R^2 of 0.162 and low GCS [p = 0.046] with an R2 of 0.061. There was positive correlation between QTc level and amount of OP compound ingested at p<0.01 and total dose of atropinization at p<0.01.

Correlations										
			QTc	BMI	S. ACHE	POP SCORE	GCS	DOSE_OF ATROPINIZATION	AMOUNT INGESTED IN ml	SBP
spearman's correlation	**QTc**		**1.000**	**.295***	**-.419****	**.530****	**-.26***	**.623****	**.466****	**-.28***
			.	**.016**	**.000**	**.000**	**.029**	**.000**	**.000**	**.024**
*. Correlation is significant at the 0.05 level (2-tailed).										
**. Correlation is significant at the 0.01 level (2-tailed).										

Overall prevalence of QT prolongation in organophosphate poisoning from studies conducted by different authors were 55.5%[8], 43.5%[4], 35.4%[3], 59.5%[2] and 28%[9] which are comparable with my results. Prevalence of prolonged QTc in my study is 33.3% when considering overall normal QTc to be less than 440ms and 31.9% when considering separate normal value of QTc in male (less than 430ms) and female (less than 450ms). Yusuf Yurumez, MD and colleague[8] found QTc prolongation in 55.5% of cases but they failed to prove it as prognostic marker in organophosphate poisoning. Shou-Hsuan and colleague[41] found hypotension to be more common in group with prolonged QTc interval and higher incidence of hypotension, respiratory failure, comma and shortness of breath in non-survivors. They did not talk much about vasopressors requirement, ICU admission, and ventilator requirement and failed to describe particular respiratory complications developed during admission which were culprit for causation of respiratory failure. While in my study, 22.7% were found to have low blood pressure (<110/70mmhg)[42] among which 78.9% required vasopressor support. Mean QTc among those with low blood pressure was significantly higher (mean = 441.19 ms, SD = 32.88) than among those with normal blood pressure (mean = 419.53, SD = 45.92) at p = 0.044. While comparing with normal QTc group, prolonged QTc group has significantly higher rate of complications developed during course of treatment; ARDS (1.5% vs 0%), Aspiration pneumonia (7.6% vs 4.5%), bed sore (1.5% vs 0%), septic shock (3% vs 0%) [p<0.001].

In another study conducted by Kumiko, Taira and colleague[7], they found prolonged QTc in 2 of 3 severe cases, 4 of 11 moderate cases and 16 of 25 mild cases. While in my study, 13(19.7%) among mild poisoning (POP Score = 0-3) and 9(13.6%) among moderate poisoning (POP Score = 4-7) had prolonged QTc. According to ACHE severity, Prolonged QTc was found in 8 among severe poisoning (ACHE = 0-700 U/L), 8 among moderate poisoning (ACHE = 700-1400 U/L) and 3 among mild poisoning (1400-3500 U/L). While comparing across ACHE severity group, 4 patients had deranged LFT among severe poisoning group and 2 patients had deranged RFT. Regarding vasopressors support, 7 among severe poisoning group and 9 among moderate poisoning group required vasopressor support. Regarding ICU admission, 9 among severe poisoning group and 9 among moderate poisoning group required ICU admission. Altogether 6 among severe poisoning group developed Aspiration Pneumonia, 1 among moderate poisoning group developed ARDS and 2 among severe poisoning group required mechanical ventilation as well. In another study conducted by Stefek Grmec, MD PHD and colleague[5], they found prolonged QTc of 83.8% in group with respiratory failure and 47.1% in group without complications, 85.3% in those requiring intubation and 41.9% in those not requiring intubation. Furthermore, they found GCS <8 in 78.3% of those requiring intubation with respiratory failure and 45.4% of those requiring intubation without respiratory failure. In my study, I found that 27(40.9%) needed ICU admission among which 48.1% had normal QTc interval and 51.8% had prolonged QTc interval (18.5% male and 33.3% female) at p = 0.005. Regarding vasopressor support, 19(28.8%) required vasopressor support, among which 31.6% had normal QTc interval and 68.5% (21.1% male and 47.4% female) had prolonged QTc interval at p = <0.001. Regarding respiratory complications, 8(12.1%) developed Aspiration Pneumonia,

among which 62.5% (25%male and 37.5% female) had prolonged QTc interval at p = 0.006. Regarding GCS and POP score, 2 females with GCS = 9-13 and 9 patients (2male, 7 female) with POP Score = 4-7 had prolonged QTc interval. In a study conducted by A. Baydin and colleague[3], they found negative correlation between QTc interval and blood ACHE level (r = -0.22, p < 0.005). My study also gave similar results. There was negative correlation between QTc and ACHE level (r = -419, p < 0.01), QTc and SBP (r = -28, p = 0.024), QTc and GCS (r = -.26, p = 0.029). There was positive correlation between QTc and POP Score (r = 0.530, p < 0.01). There was also positive correlation between QTc level and amount of OP compound ingested at p<0.01 and total dose of atropinization at p<0.01.

Limitation of study:

1. Short duration of study due to time constraint of the residency programme.
2. Since this study is conducted mainly at Bir Hospital, hence racial variation in presentations, complications and outcome of organophosphate poisoning could not be evaluated.
3. Sample size is small. It could have been better to predict morbidity and mortality pattern on the basis of prolonged QTc interval with large sample size.
4. Most of the participants were from lower socio-economic conditions, so due to financial issue, serial monitoring of some needed lab parameter could not be done.
5. Due to unavailability of sufficient ICU bed, some of patient with indication of ICU admission has to be managed in General Ward.

Conclusion:

Patients with prolonged QTc have significantly higher POP score, lower GCS, long hospital stays, higher complications rate, more ICU requirement, and more vasopressors requirement. Hence QTc prolongation is a bad prognostic marker in organophosphate poisoning.

Recommendation:

Since patients with prolonged QTc have significantly higher POP score, lower GCS, long hospital stays, higher complications rate, more ICU requirement, and more vasopressors requirement. Hence, we recommend QTc prolongation as a bad prognostic marker in organophosphate poisoning and QTc must be calculated at admission and during the course of treatment to predict outcome in organophosphate poisoning.

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