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The Study of Prolonged QTc Interval as a Predictor of Outcome in Patients Admitted With Medical Emergencies

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ABSTRACT

Background: To study the QTc interval in patients admitted as medical emergencies and to predict in-hospital outcomes of the patients. **Methods:** Prospective observational study carried out in 312 patients admitted in our hospital with acute medical emergency. Clinical, echocardiographic and laboratory profile and in-hospital outcome of patients with medical emergencies were assessed as a part of work up. QTc interval was calculated by using Bazzets formula with in 24hrs of admission by using standerd 12 lead ECG. Patients with QTc ≥0.44 sec in male and QTc ≥0.46 sec in females were taken as the cutoff value for prolonged QTc interval and values were compared with outcome and duration of stay in hospital. The patients during hospital stay and were observed for outcome like duration of stay ,development of major complications or worsening of symptoms ,and death were assessed in relation to the QTc interval. **Results:** Prolonged QTc interval ≥ 0.44sec in male and ≥ 0.46sec in female was observed in 113 patients (36.2%). In the study 137(43.9%) patients had cardiovascular emergencies in which 55(48.7%) patients had prolonged QTc,112(35.9%) had presented with neurological emergencies among them 34(30.1%) patients had prolonged QTc,66(21.2%) patients had respiratory emergencies showing QTc prolongation in 27 (23.9%) patients,28(9%)patients had presented with gastrointestinal emergencies have 9(8%) patients with prolonged QTc,35(11.2%) patients had renal emergencies had 9 (7%) patients with long QTc,12(3.4%) patients had endocrine emergenicies like DKA and HHS had 5(4.4%) patients with long QTc .outcome of the patients showing duration of stay was prolonged and deaths were relatively high in patients with long QTc. **Conclusion:** Prolonged QTc interval was found to be an important predictor of in-hospital outcome of the patients with prolonged QTc were showing bad outcome when compared with the patients with normal QTc interval in terms of duration of stay, improvement and death.

Keywords: Medical Emergency, QTc interval.

INTRODUCTION

Electrocardiogram is a invaluable and easily available bedside non-invasive tool in assessing acutely ill patients. Of all the ECG measurements QT interval is one of the important predictors of outcome in critically ill patients.[1] The QT interval represents the onset of electrical depolarization of the ventricles to the end of repolarization of the heart. This interval is measured from the beginning of the QRS complex to the end of the T wave. It is influenced by both physiological and pathological factors including emotional stress, gender, obesity, food consumption, and electrolyte disturbances, as well as diseases of the heart muscle and coronary artery disease. Various drugs can also cause prolonged QT interval which are commonly used in critically ill patients.[2]

QT interval varies inversely with heart rate and is therefore corrected by formulas that take this variation into account; the corrected interval is designated "QTc". The cause of prolongation may be multi factorial but is generally congenital (e.g., long QT syndrome) or acquired (e.g., induced by medications).QTc can be calculated by Bazett's formula QT/RR. QTc prolongation is defined as QTc interval of more than 440 ms for men and that of 460 ms for women.[3]

Patients admitted as medical emergencies has variety of age group and primary disease. These patients have high morbidity and mortality. The acutely ill patients are at increased risk of developing prolonged QTc and Torsedes de pointes due to risk factors, such as renal or hepatic dysfunction, electrolyte abnormalities, brady arrhythmias and increased exposure to drugs causing prolonged QTc interval.[4]

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MATERIALS AND METHODS

Source of Data

Patients admitted with 'acute medical emergencies' at B.L.D.E.U'S Shri B.M. Patil Medical College Hospital and Research centre, Vijayapur between December 2017 to August 2019.

Inclusion criteria:

Patients with Acute medical emergencies

Exclusion Criteria

1. All cardiac arrhythmias
2. Patients age less than 18 yrs

Methodology

To determine the clinical outcome of the patient in relation to the prolonged QTc interval in patients who has admitted to the BLDE hospital with acute medical emergency, a standardized assessment will be performed.

Clinical history and examination, electrocardiogram at admission, cardiac enzymes-Troponin I, CPK MB, Echocardiograhy, CT/MRI brain, ABG analysis and other relavent laboratory investigations were done. QT interval was calculated for all the patients who admitted with medical emergency with in the 24hr of admission .QT interval was corrected with heart rate by using Bazzets formula, which is most commly used for the QTc calculation. A 12 lead ECG will be done using BPL CARDIART 6108-T ECG machine and ECG will be analysed. The QT interval was calculated from V3 lead .if lead led V3 was not clear V2 followed by lead 2 was preferred. The formula to calculate QTc is mentioned below.

Bazzets formula = $\frac{QT}{\sqrt{RR}}$

Statistical analysis:

All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean± standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and diagrammatic presentation. Chi-square ($\chi 2$) test was used for association between two categorical variables.

The formula for the chi-square statistic used in the chi square test is:

$$\chi_c^2 = \sum \frac{(O_i - E_i)^2}{E_i}$$

The subscript "c" are the degrees of freedom. "O" is observed value and E is expected value.

If the p-value was < 0.05, then the results were considered to be statistically significant otherwise it was considered as not statistically significant. Data were analyzed using SPSS software v.23.0. and Microsoft office 2007.

RESULTS

Table 1: Distribution of Cases According to Symptoms

Major Presenting Symptoms	N	%
Breath Lessness/Chest Pain	84	26.9
Vomitting And Headache	27	8.7
Cough	25	8.0
Consumption Of Unknown Compound	22	7.1
Abdominal Discomfort	19	6.1
Fever	13	4.2
Giddiness	13	4.2
Swelling Of Both Lower Limbs	12	3.8
Abdominal Distension	12	3.8
Loose Stools	8	2.6
Involuntary Movements In Upper And Lower Limbs And Weakness Of Limbs	7	2.2
Chest Pain	15	1.0
Discolouration Of The Eyes	1	0.3

In our study, the total number of patients enrolled were 312, of which 67.6% were males and 32.4% was female patients. The mean age of the patients enrolled in our study was 53.5 (±19.2) years, with minimum age 18 and maximum age 99 years. The major presenting symptom reported in our study was breathlessness 26.9%. In the patients attending the ED, the system involved were CNS 35.9%, CVS, 43.9%, GI/hepato-biliary 9%, respiratory system 21.2%, renal 21.2%, endocrinology 3.2% and hematology 0.3%. The distribution of patients as per ABG were: acidosis 21.8%, alkalosis 10.3%, CO2 retention in 1.9% cases.

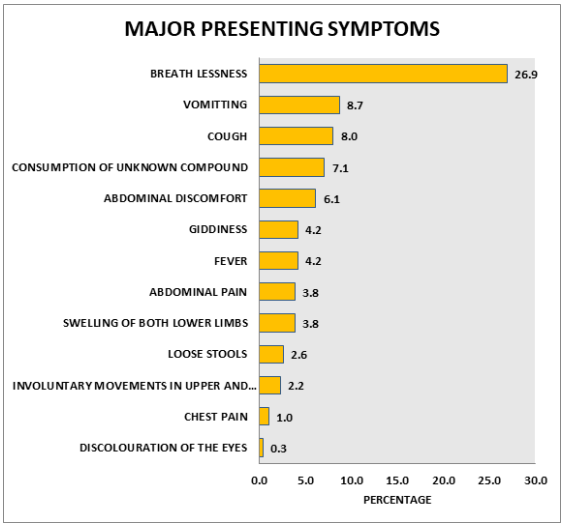

Figure 1: Distribution of cases according to symptoms

Table 2: descriptive statistics of pathological parameters

	Min	Max	Mean	SD
Haemoglobin	4.2	18	12.6	6.6
Total Wbc Count	1080	57640	13877.3	7938.9
ESR	1	134	32.8	31.8
Rbs	36	525	144.7	103.7
Sr.Creatinine	0.5	12	1.7	2.2
Sr.Sodium	103	154	133.8	20.9
Sr.Potassium	1.3	6.4	4.4	3.6
Cpk-Mb	3.0	300	46.6	64.5
Troponin-I	0.012	40000	2864.2	8977.5

Out of 312 patients study group 112 patients(35.9%) were presented with the complaints of central nervous system ,137 patients (43.9%)had presented with the involvement of cardiovascular system ,66 patients(21.2%) presented with involvement of respiratory system ,28 patients(9%) had presented with symptoms of gastrointestinal system involvement,35 aptients (11.2%)had presented with renal emergencies and 10 patients (3.2%)had presented with endocrine involvement.

Table 3: distribution of cases according to QTc

QTc	N	%
Prolonged	113	36.2
Not Prolonged	199	63.8
Total	312	100.0

Out of 312 patients the QTc interval prolongation within 24 hrs of admission .113 patients had

prolonged QTc interval which is more than 0.44 sec in males and more than 0.46 in females.shortest was 0.24 sec and longest was 0.74 with a mean of 0.44 sec

Table 4: descriptive statistics of QT

	Min	Max	Mean	SD
QT	0.20	0.68	0.4	0.1
QTc INTERVAL	0.24	0.74	0.44	0.1

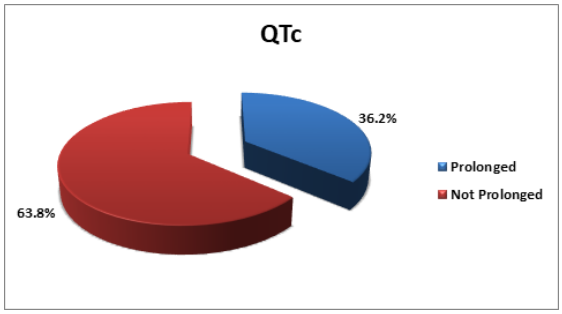

Figure 2: distribution of cases according to QTc

QTc interval was analysed in a different systems and values were compared with different system. QTc interval of 112 patients with CNS involvement was observed 34 had prolonged out of 112. Cardiovascular system involvement was observed in 137 patients, 55 patients had prolonged QT interval .66 patients were admitted with respiratory emergency 27 patients had prolonged QT interval.35 renal emergencies were observed for QT prolongation only 9 had prolonged,28 patients presented with gastro intestinal emergencies in that 9 ptients had presented with prolonged QTc. 10 patients had endocrine emergencies like DKA ,5 patients had prolonged QTc

Table 5: distribution of system involved according to QTc

System involved	QTc			
	Prolonged		Not Prolonged	
	N	%	N	%
CNS	34	30.1	78	39.2
CVS	55	48.7	82	72.6
Gi/Hepatobiliary	9	8.0	19	16.8
RS	27	23.9	39	34.5
Renal	9	8.0	26	23.0
Endo	5	4.4	5	4.4

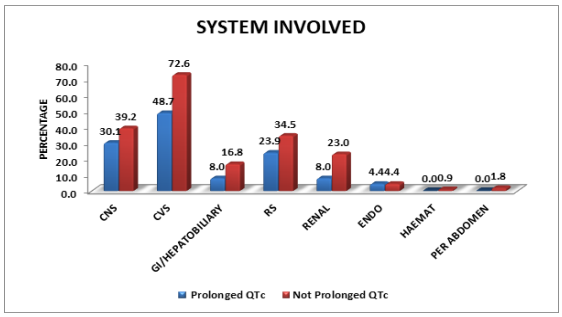

Figure 3: distribution of system involved according to QTc

Among 312 patients duration of stay was compared with prolonged QTc interval.among 16 patients who stayed for less than 24 hrs QTc was prolonged in 5 patients.76 patients were discharged in 2-3 days 21 patients had prolonged QTc, 132patients were discharged between 4-7 days of admission56 patients had prolonged QTc, 66 patients had discharged between 7-10 days 26 had prolonged QTc and 23 patients were admitted for more than 10 days and QT was prolonged in 5 patients.

Table 6: distribution of duration according to QTc

Duration	QTc				p value
	Prolonged		Not Prolonged		
	N	%	N	%	
≤24 HRS	5	4.4%	11	5.5%	0.146
2-3 DAYS	21	18.6%	55	27.6%	
4-7 DAYS	56	49.6%	76	38.2%	
7-10 DAYS	26	23.0%	40	20.1%	
>10 DAYS	5	4.4%	17	8.5%	
Total	113	100.0%	199	100.0%	

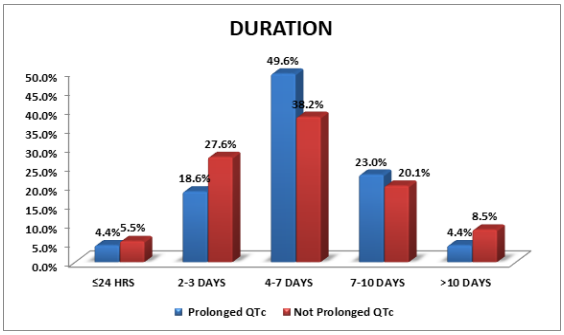

Figure 4: distribution of duration according to QTc

Table 7: distribution of outcome according to QTc

Outcome	QTc				p value
	Prolonged		Not Prolonged		
	N	%	N	%	
AMA/DOR	0	0.0%	5	2.5%	0.200
Death	20	17.7%	21	10.6%	
Improved	78	69.0%	143	71.9%	
Not improved/ prolonged	13	11.5%	27	13.6%	
Referred	2	1.8%	3	1.5%	
Total	113	100.0%	199	100.0%	

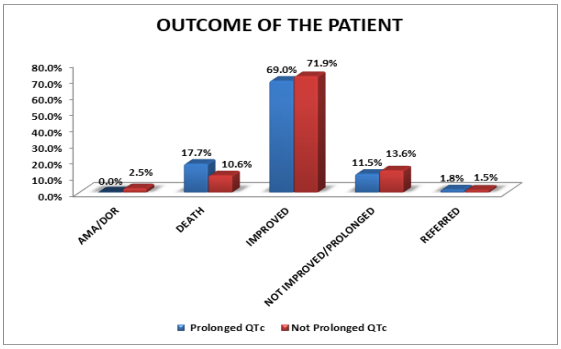

Figure 5: Distribution of Outcome According to QTc

Outcome of 312 patients were observed during the study and outcome was compared with the QTc interval.41 patients were died during the study 20 had long QTc, worsened or unchanged outcome was

observed in 40 patients and 13 had long QTc, 221 patients were improved with 78 patients had prolonged QTc and 10 patients were referred or went against medical advice during study.

DISCUSSION

This study was conduct to evaluate the QTc interval in medical emergency patients and their in-hospital outcomes. Since ECG is available and relatively non-invasive and cheap, knowledge of QTCis of immense benefit in patient management.[5]

The risk assessment for QT prolongation of in-hospital patients is based on their medication profile, demographic risk factors, electrolyte disturbances, and monitoring of the corrected QT (QTc) interval. Large population studies have shown a relation between QTc and all- cause mortality, cardiac mortality, and sudden cardiac death.[6,7] A normal corrected QT (QTc) for women is less than 0.46 seconds and for men is less than 0.44 seconds. A QTc of greater than 0.50 seconds in either gender positively correlates with a higher risk for TdP. The duration of QTc is a reliable risk indicator of cardiac events. Therefore, patients with long QT syndrome and associated ventricular arrhythmias should receive QT monitoring in the ED (class I recommendation).[8,9]

In our study the mean QTc interval observed was 0.5 (±0.1) with range of minimum 0.24 to maximum 0.74.The importance of QT monitoring in the ED cannot be underestimated because ED patients are uniquely at risk for developing TdP owing to their vast array of chief complaints and high acuity. Specific patient characteristics are associated with development of TdP and should be considered during triage and risk stratification.[10] Practice guidelines recommend measuring patients' QT/QTc interval at baseline and documenting repeat measures at least once every 8 hours.[11] Patients in the ED may initially require QT/QTc monitoring more frequently, especially if receiving medications known to prolong the QT interval.

The prevalence of QTc prolongation is higher in patients brought to ED owing to presence of acute ailments. Frequently they have one or more of risk factors and are on poly-drug therapy. In this study the prevalence of prolonged QTc interval was 36.2%, which was similar to earlier studies by Birda et al. and Seftchick MW et al.[12,13] In the study done by Birda et al the prevalence of QTc prolongation was 34.1%. In this study QTc prolongation was observed in 17.7% patients who succumb to the disease, 69% patients with improvement, 11.5 % who did not improve, and 1.8% referred patients. Whereas in a study by Birda et al, there was no difference in hospital mortality at subgroup analysis. Patients with markedly prolonged QTc interval had significantly more episodes of in-hospital ventricular tachycardia and hospital mortality.[14] In a recent study, the most frequent ECG abnormality (18%) was prolonged QTc interval.[15] High prevalence of Prolonged QTc (35%) was also reported by George TK et al in medical ICU at admission.[16]

The cardiovascular systems (CVS) involvement according to QTc prolongation was found in 48.7% cases. In our study ST segment changes observed were as follows: depression 9.6%, elevation 17.9%, isoelectric 71.2%, saw tooted flutter waves 0.3%, T inversion inV1 to V3 0.3% and no change in 0.6%. In all the patients the rhythms was regular and regional wall motion abnormality was found in 15.1%. LVEF was found to be less than 45% in 10.5% of study patients. The QTc interval was prolonged in 100% patients with early transmural ischemia. When compared with clinically accepted indexes of transmural ischemia (i.e., STD and STE [≥1 mm] it is the earliest noted ECG abnormality.[18] The corrected QT interval (QTc) is prolonged in the setting of acute coronary artery disease.[19]

Our results show QTc prolongation in 30.1% patients with CNS involvement. QTc-prolongation is common after posterior circulation stroke and is also associated with temporal lobe infarction.[20] Our finding demonstrated QTc prolongation in 8% of patients having renal involvement and with mean sr. creatinine 1.9 (±2.3). The QTc prolongation was also observed in 36.3% patients with sr. creatinine > 1.2. Hemodialysis patients have tendency to have higher values of QTc.[20] QT interval prolongation is a predictor of sudden cardiac death due to ventricular arrhythmias, which may account for 1.4% to 25% of deaths in end-stage renal disease (ESRD).[21]

Overt hypothyroidism is associated with many cardiac manifestations, such as prolongation of QRS and QT intervals. QT prolongation and increased QTd have been shown to be directly related to TSH level in overt hypothyroidism.[22] Paradoxically, hyperthyroidism can also lead to QT prolongation. In adults with hyperthyroidism, QTc is prolonged compared with controls that tends to normalize with treatment of hyperthyroidism.[23-25] QTc prolongation observed at baseline in type 2 diabetic (T2D) was significantly associated with QTc prolongation during severe hypoglycemia (SH) in patients with T2D, indicating the need of QTc monitoring and measures to be taken to avoid SH.[26] Prolongation of the QTc has been described in a few children receiving ketogenic diets. But cardiac effects of ketosis have not otherwise been investigated. Prolonged QTc occurs frequently during DKA and is correlated with ketosis.[27] But the findings regarding the QT and QTc interval durations are a little bit controversial in type 1 diabetes.[28,29]

Prolonged QTc (corrected QT) interval and torsades de pointes (TDP) are associated with hypocalcemia, hypomagnesemia, hypokalemia, possibly alkalosis and may result in syncope and sudden cardiac death. In this study QTc prolongation was observed in patients with mean Sr. potassium 4.2 (±0.9). The

QTc prolongation was observed in 17.7% patients with sr. potassium < 3.5. QTc duration is highly sensitive to hypokalemia, particularly in women. Methadone prolongs QTc remarkably compared to other non-cardiologic medicines. QTc>500 with normal QRS often signifies profound illness and substantial mortality risk, though not necessarily imminent TdP.[30] Hypokalemia is associated with lengthening of QT interval in psychiatric patients on admission and it is a strongly recommended as screening test.[31] Drugs known to prolong the QTc interval should be discontinued immediately. Serum potassium and/or magnesium should be replaced if the patient is hypokalemic or hypomagnesemic.

Numerous drugs have been associated with QT prolongation and over the last decade a number of drugs have been withdrawn from the market or restricted because of reports of QT prolongation and TdP.[32] In this study out of the 312 patients, 156 (50%) were on drugs with potential to cause QTc prolongation. Among these 156 patients, 43(30%) had QTc prolongation. Another study reporting comparable prevalence of QTc proportion had significant number of patients on drugs with potential of prolonging QT interval. Study by Tisdale et al observed that among patients with a prolonged QTc at admission 18 (35%) received a QT prolonging drug.[33] In other studies 34.7% of the population with a prolonged QTc received a QT prolonging drug.[34] It was noted that an additional QT prolongation of >60 ms occurred in 57.1% of these patients. The study by Kozik and Wung documented that 59% received a drug with known QT prolonging action.[35] Some evidence indicates that concomitant administration of ≥ 2 QTc interval–prolonging drugs may increase the risk. Conditions that lead to elevated plasma concentrations of QTc interval–prolonging drugs increase the risk of drug-induced TdP. These include pharmacokinetic drug interactions, inadequate dose adjustment if the drug has renal elimination and QTc interval–prolonging drugs in patients with acute kidney injury or chronic kidney disease.[36]

In respiratory system disorder, mortality of COPD patients is associated with QTc interval. (37)The study by Taooka Y et al showed that QTc interval (> 0.44 seconds) is one of the potential prognostic factors for pneumonia in elderly patients.(38)In our study QTc prolongation observed in 23.9% with respiratory system involvement.

During present study, the mean duration of stay in the emergency department was 3.4 (±1.1) days ranging from minimum 1 day to maximum 16 days. The duration of QTc prolongation was ≤24 hrs. in 4.4% of patients, 2.-3 days in 18.6% of patients, 4-7 days in 49.6% of patients, 7-10 days in 23.% of patients, and > 10 days in 4.4% of patients. In study by Bidra et al the median duration of hospital stay was 6 days. Whereas, George TK et al documented the mean duration of stay in the Intensive care unit (ICU) as 7 days and hospital stay of 13 days. The duration of ICU stay was comparable between normal QTc vs prolonged QTc group, 7.2 and 7.3 days respectively. In our study too, the duration of ICU stay for QTc prolonged group was not significantly different as compared to normal QTc group.

The QT prolongation due to existing cardiovascular disorder has been shown to have association with poor ICU outcomes. However earlier studies demonstrated mixed results in terms of outcome in hospital admissions with prolonged QTc interval. The outcome of the patient observed was, discharge against medical advice in 1.6%, death in 13.1%, improvement in 70.8%, prolonged illness in 12.8% and referral of 1.6%. In our study QTc prolongation resulted in mortality in 17.7% patients, and there was improvement in 69% patients. About 11.5 % patients had worsening and 1.8% patients were referred. Our results were in congruence with find of study by Bidra et al.[39] The results of Bidra et al show discharge at recovery in 76%, hospital death in 18.25%, leave against medical advice in 4.9% and two patients (0.76%) absconded. Our patient mortality rate was lower than the results of Anderson et al (all-cause mortality 39%) for patients with QT prolongation. The probable reason of findings by Anderson et al could be higher rate of ventricular arrhythmias patients in their cohort.[40] Seftchick MW et al reported structural heart disease, renal failure, and stroke as the most common comorbidities. About 44% of patients with any degree of QTc prolongation were discharged from the ED. Furthermore, 23% of patients with QTc intervals ≥ 500 ms were discharged from the ED, including 16 patients with QTc intervals greater than or equal to 500 ms and QRS durations less than 120 ms (16/60; 27%). Five percent of the patients with QTc prolongation died in the ED or during hospitalization; none had QTc prolongation or torsades de pointes listed as a cause of death.[1] It is seen that in acutely ill patients the prevalence of a prolonged corrected QT interval (QTc) is much higher than one might expect. Though the underlying causes may be correctible.

CONCLUSION

To conclude, a high prevalence of QTc prolongation was present in patients admitted to our medical emergency department along with high incidence of risk factors. Therefore, it is critical that emergency department staff should not only be cognizant of drugs prolonging QTc, but must also thoroughly elicit related patient history that may contribute to QTc prolongation and monitor patients with risk factor for better patient outcomes.

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