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OCCURRENCE OF QTC INTERVAL PROLONGATION AMONG HEPATITIS C PATIENTS

Dr. Joham Javed[1], Dr. Ahmad Moosa Kazi[2], Dr. Mohammad Ali Khalid[3]

[1, 2, 3] Holy Family Hospital, Rawalpindi

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Abstract:

Objective: *The aim of our study is to determine frequency of QTc interval prolongation in hepatitis C infection. To associate QTc interval prolongation in patients having cirrhotic and non-cirrhotic chronic hepatitis c infection*

Study design: *Descriptive Case Series*

Place and Duration: *The study was conducted in Medical Unit of Benazir Bhutto Hospital, Rawalpindi for the duration of one year from September,2018 to August, 2019.*

Methodology: *Patients suffering from chronic hepatitis c infection with cirrhosis was taken from medical ward and non-cirrhotic chronic hepatitis c infection was taken from general medical OPD. Consent was taken. ECG technician performed ECG for QTc interval calculation. Information was recorded on the form. The variable of interest was age, gender, cirrhosis, QTc interval and comparison of prolongation of QTc between hepatitis c positive cirrhotic and non-cirrhotic patients.*

Results: *Total 110 patients were included according to the inclusion criteria of the study. Mean age (years) in the study was 56.84+11.05. There were 48 (43.6) male and 62 (56.4) female patients who were included in the study according to the inclusion criteria. Mean duration of QTc interval was 0.48+0.04. Out of 110 patients, there were 27 (24.5) patients who have prolonged QTc interval. The frequency of QTc interval prolongation in patients with cirrhotic and non-cirrhotic chronic hepatitis C infection was 22 (57.9) and 05 (6.9) respectively which was statistically significant (p-value 0.000).*

Conclusion: *The study concludes that QTc interval prolongation in cirrhotic patients was high which showed that cirrhotic patients are at risk of developing ventricular arrhythmias due to cardiomyopathy, so a simple ECG test can be used to diagnose and prevent cardiac events in cirrhotic patients as it is simple as well as easily available.*

Keywords: *Cirrhosis, Hepatitis C, Prolonged QT interval, non-cirrhotic Chronic Hepatitis C Infection*

Corresponding author:

Dr. Joham Javed,

Holy Family Hospital, Rawalpindi

QR code

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INTRODUCTION:

Cirrhosis is caused by hepatocellular injury by HBV, HCV, HDV, autoimmune hepatitis; alcoholic and nonalcoholic steatohepatitis, Wilson's disease, alpha1-antitrypsin deficiency and certain medications for example anti tuberculous drugs [1]. Liver Cirrhosis is the most documented cause of hospitalization and death in the world. It is one of the commonest causes of mortality and morbidity in Pakistan mainly due to hepatitis C infection [2]. Cirrhosis causes cardiomyopathy which results in poor contraction and relaxation of the heart that results in electrophysiological changes evident on ECG. ECG changes include prolongation of QTc (corrected QT interval), tachycardia, impaired myocardial contractility [2]. The corrected QTc interval that is prolonged is directly proportional to the severity of cirrhosis and reversible after transplantation of liver. So, it can be used as a marker of disease severity and it may cause cardiac arrhythmias in liver cirrhosis [3].

A lengthy QT interval causes an increased risk of ventricular arrhythmia, particularly polymorphic ventricular tachycardia. This may result into ventricular fibrillation and sudden death. Therefore, calculating corrected QT-interval help us to identify those patients who are at increased cardiovascular risk because of liver cirrhosis [4]. Previous studies showed 32% patient with cirrhosis have prolong corrected QT (QTc) interval as compared to 2.5 to 5.7 of the non-cirrhotic hepatitis C patients ($p< 0.001$) [5]. Frequency of QTC that is prolonged in patients with liver disease reveals 53(22.08) while 187(77.92) had no prolongation of QTC interval among patients with chronic liver disease [6].

Prescribers need to take caution by getting insight about drugs that are already being implicated, especially if the drug in use prolongs the QT interval or if the patient has a condition associated with QT prolongation. Many drugs can prolong the QT interval of the electrocardiogram (ECG). The QT interval are representative of ventricular electrical depolarization and repolarization. A QT interval that lengthens is an indicator of potential ventricular tachyarrhythmias such as torsade's de pointes or risk factor causing sudden death [7].

Heart rate is determinant of the QT interval as R-R interval in an evident way (faster heart rate exhibits shorter R-R Interval and QT interval) and adjusting it might enhance the chances of detecting patients at increased risk of ventricular arrhythmia. Commonly, for measuring QT interval, lead II for serial ECGs evaluation is considered, having leads I and V5 being comparable alternatives to lead II. Leads III. While, aVL and V1 are not normally viable for measuring [8]. Subjectivity is observed while measuring the QT interval accurately [9] owing to the reason that the conclusion of the T wave is not well defined in most cases and merges gradually with the baseline usually. In an ECG complex, QT interval can be obtained manually by applying various methods like the threshold method (the point at which the component of the T wave merges with the isoelectric baseline determines the end of the T wave) or the tangent method (the end of the T wave is determined by where the tangent line extrapolated from the T wave at the point of maximum downslope intersects with the isoelectric baseline) [10].

Measuring QT can also be performed by the method called 'superimposed median beat' because of the access availability of digital ECGs with simultaneous 12-channel recording. In this method, for each of the 12 leads, construction of a median ECG complex take place. These cumulative beats are superimposed on each other and we can measure the QT interval either from the earliest onset of the Q wave to the latest offset of T wave or by considering the point where maximum convergence for the Q wave onset to the T wave offset occurs [11].

QTc prolongation that is induced through medication is not a universally observed phenomenon. The reason behind why some people are more vulnerable to this condition than others is yet elusive. There might be a possibility of subclinical genetic mutation that express itself when it is exposed to certain drugs. Taking notes about the history of syncope or cardiac arrest is mandatory before prescribing a drug associated with prolonged QTc. Also, a detailed history of occurrence of syncope, unexpected death at a younger age or inherited deafness (a Jervell and Lange-Nielsen syndrome characteristic) in family is to be included. Further, a confirmatory 12 lead ECG should be administered for any doubt of a congenital long QTc syndrome. Drugs which could worsen the condition should be avoided if the ECG shows prolongation of the QTc interval [12]. QTc interval should be observed in patients who presents history of syncope or cardiac arrest. It is suitable to perform a 12 lead ECG within the first few days of treatment to look for QTc prolongation beyond devised limits when a high-risk patient is prescribed with an implicated drug. It is apt to stop the offending drug or take an alternative drug that does not affect the interval if QTc prolongation is observed [12].

As QTc interval prolongation shows that cirrhotic patients are at risk of developing ventricular arrhythmias due to cardiomyopathy, so a simple ECG test can be used to diagnose and prevent cardiac events in cirrhotic patients as it is simple, easily available as well as cost effective.

METHODOLOGY:

Non probability consecutive sampling was used for the patient's data collection in the study. Total 110 patients were enrolled in study by using WHO formula, following are the calculation; confidence level = 95%, anticipated population proportion = 22.06, absolute precision required = 8%. Those patients who have qualitative HCV PCR positive were considered as chronic hepatitis-C infected patients. Cirrhosis is a chronic liver disease, caused because of some liver tissue damage resulting in scarring of the liver (fibrosis - nodular regeneration) causing ascending decrease in liver function, excess of fluid in the abdomen (ascites) diagnosed clinically by shifting dullness and fluid thrill, bleeding disorders (coagulopathy) diagnosed by upper or lower gastrointestinal bleed and deranged PT, augmented pressure in the blood vessels (portal hypertension) causing variceal bleeding and Ultrasound shows coarse liver echo texture. QTc interval prolongation is diagnosed on ECG while QT interval is correctly inculcated through Bazett's formula:

$$QTc=QT/\sqrt{RR}$$

Whereas, QTc >.0.44 in females and > 0.46 in males considered to be prolong. Patients having chronic hepatitis-C infection with and without cirrhosis having between ages 25 - 70 years from either sex were included in the study. Those patients who are having structural or non-structural heart disease like valvular or ischemic heart disease, patients who are taking drugs which effect QT interval and patients with hepatocellular carcinoma on USG were considered as an exclusion criterion. Patients having chronic hepatitis c infection with cirrhosis was taken from medical ward and non-cirrhotic chronic hepatitis c infection was taken from general medical OPD. Consent was taken. For QTc interval calculation ECG was performed by ECG technician. Information was recorded on the form. The variable of interest was age, gender, cirrhosis, QTc interval and comparison of prolongation of QTc between hepatitis c positive cirrhotic and non-cirrhotic patients.

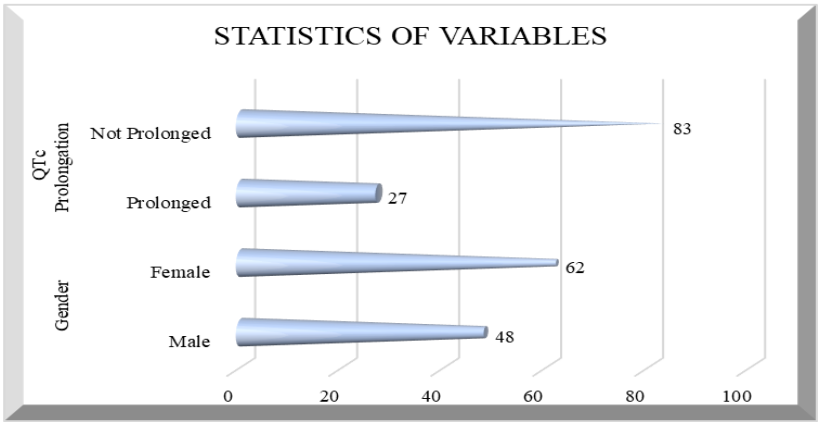
Data was entered and analyzed using SPSS 20. Mean and standard deviation was calculated for age, QTc interval. Frequencies and percentages were calculated for qualitative variables like QTc prolongation in both the cirrhotic and non- cirrhotic groups and gender of patient. Chi-square test was applied to compare frequency of QTc prolongation in cirrhotic and non-cirrhotic hepatitis C patients. P-value $\leq$ 0.05 was significant.

RESULTS:

Data was entered and analyzed in SPSS version 20. Total 110 patients were included according to the inclusion criteria of the study. Mean age (years) in the study was 56.84+11.05 whereas there were 48 (43.6) male and 62 (56.4) female patients who were selected for the study according to the inclusion criteria. Mean duration of QTc interval was 0.48+0.04 in the study. Frequency of QTc interval prolongation in hepatitis-C infection patients was assessed among 110 patients. Of these, 27 (24.5) patients have prolonged duration of QTc interval, as shown in Table. I

Table No 01: Descriptive Statistics of Variables

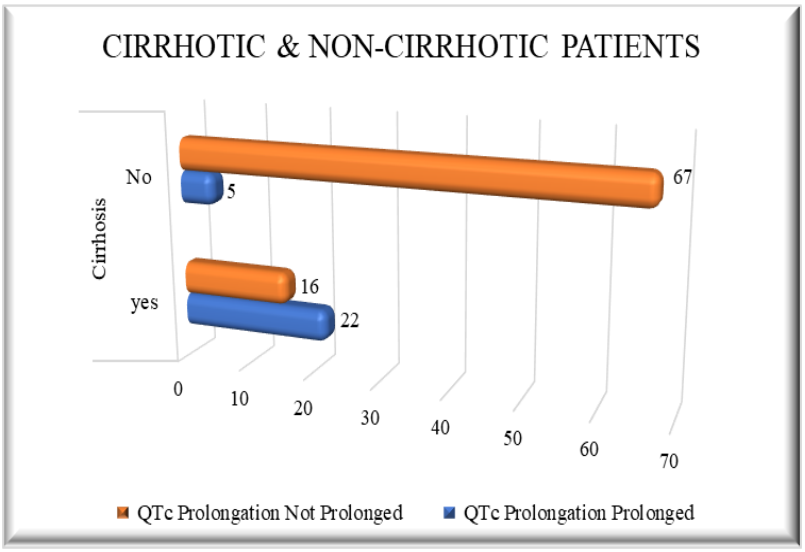
Variables		Qty	%age
Age (years)	Mean±SD	26.58+11.05	
QTc interval	Mean±SD	0.48+0.04	
Gender	Male	48	43.6%
	Female	62	56.4%
QTc Prolongation	Prolonged	27	24.5%
	Not Prolonged	83	75.5%



Frequency of QTc interval prolongation in patients with cirrhotic and non-cirrhotic chronic hepatitis-C infection. There were 22 (57.9) cirrhotic patients who were found prolonged QTc interval whereas there were 05 (6.9) non-cirrhotic patients who were found prolonged QTc interval which was statistically significant (p-value 0.000), as shown in Table. II

Table No 02: Comparison of QTc prolongation among Cirrhotic & Non-Cirrhotic patients

Variables		*Cirrhosis*				*P-value*
		yes		No		
		Qty	%age	Qty	%age	
QTc Prolongation	Prolonged	22	57.9%	05	6.9%	0.000
	Not Prolonged	16	42.1%	67	93.1%	
Total		38	100%	72	100%	



DISCUSSION:

Cirrhosis liver is a chronic ailment of liver occurring due to the degeneration of liver cells subsequent to fibrosis and dysfunctional regeneration of nodules that leads to portal hypertension and complications that it entails. Cirrhosis liver was found to be the 10th and 12th prominent cause of death in men and women respectively, resulting in about 27,000 deaths as per

the records of the United States of 2001. In Pakistan, like other developing countries, cirrhosis liver has greater prevalence in comparison to countries well adjusted. So as so, hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, both are considered endemic in our community [5]. These viruses can have a causal effect leading to cirrhosis liver, hepatocellular carcinoma (HCC) and certain varied complications of cirrhosis liver resulting in enhanced indisposition and chances of death in these patients.

Worldwide, Cirrhosis liver pertaining to HCV has become a significantly major problem. It is more probable for HCV to lead to chronic symptoms as compared with hepatitis B virus (HBV). Approximately 1.5 million cases are diagnosed of HCV infection per year in US while, the prevalence of HCV infection in blood donors which are fit to donate was noted as 15 [6]. for Africa, in Japan 1.5, in US 0.64, 0.34 and 0.075 in Canada and United Kingdom respectively. Prevalence of HCV in Pakistan ranges from 00-20.89. as per different studies [13]. There are over 350 million of chronic carriers of HBV infection worldwide, among them, 75 are approximated to be from Asian subcontinent. HBV infection is 2-14 prevalent in healthy blood donors is in Pakistan [13]. Whilst, the prevalence of HCV and HBV infection is approximately 3.6-18.66 and 4.25- 7 [13]. respectively in general population. 10 to 20 of people who are heavy drinkers for a decade or more,3 alcoholic liver disease or alcoholic liver cirrhosis is found.

Chronic liver disease entails progressive destruction and regeneration of the liver parenchyma causing fibrosis, nodule formation and cirrhosis eventually. It is taken as the 10th top cause of adults' death worldwide. Ascites, portal hypertension, esophageal varices, encephalopathy, hepatocellular carcinoma, hepatorenal and hepatopulmonary syndromes are well recognized complications pertaining to chronic liver disease [3].

Many of the cardiovascular changes exemplifies chronic liver disease, such as the subtle subclinical alterations of pre-ascitic stages, the hyperkinetic syndrome observed when decompensation develops etc [14]. A prolongation of QT interval has been shown in patients with chronic liver disease and represents the most common electrocardiographic finding in this setting [15]. The QT interval is the final interval of ECG waveform, which is measured from beginning of the QRS complex to the end of the T wave in the lead with longest interval and without prominent U waves. The QT interval bears an inverse relationship with heart rate and several formulas are available for correcting the QT intervals for heart rate. The most widely used algorithm is the Bazett equation, in which corrected QT (QTc) is calculated by dividing measured QT interval by square root or R-R interval in seconds. The normal length of QTc is 0.38-0.44 sec. The QT-interval is representative of the length of systole in ventricles, and prolonged interval can provide the substrate for ventricular arrhythmias or abrupt death [6]. The frequency expected of QTc prolongation in chronic liver disease in Pakistan is 19.2. The patients of chronic liver disease with prolonged QTc interval showed higher mortality rates than those with normal QTc interval. further, prolonged QTc interval relates to the intensity of chronic disease of liver [16].

In our study, mean age (years) in the study was 56.84+11.05 with ranges from 25 to 70 years. Whereas in a study conducted by Umair et al [17], the mean age of patients in years was 55.04+4.08.

A study conducted in 2012 [3] found that the frequency and percentage of male and female patients was 49 (51.6) and 46 (48.4) respectively. Whereas in our study, there were 48 (43.6) male and 62 (56.4) female patients. Umair et al [17] in their study calculated that the mean QTc interval in patients was 0.463+0.1312. In our study, mean duration of QTc interval was 0.48+0.04. In our study, out of 110 patients, there were 27 (24.5) patients who have prolonged QTc interval. While in a study conducted by Sohail et al [6], frequency of QTC prolongation in patients with liver disease reveals frequency and percentage of 53(22.08).

CONCLUSION:

The study concludes that QTc interval prolongation in cirrhotic patients was high which showed that cirrhotic patients are at risk of developing ventricular arrhythmias due to cardiomyopathy, so a simple ECG test can be used to diagnose and prevent cardiac events in cirrhotic patients as it is simple as well as easily available.

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