JOURNAL OF RANGAMATI MEDICAL COLLEGE

Original Article

Volume 3, Issue 2, July 2020; 21-24

Relationship Between Serum Ferritin Level and Corrected QT Interval (QTc) in Transfusion Dependant Thalassemic Children

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ABSTRACT

Background: Thalassemia is the most common inherited gene disorder in the world. Transfusion is the mainstay of management. The iron burden in the body can be estimated by means of serum ferritin. Iron overload and its detrimental effects on multiple organs specially in heart is a major concern. On the other hand, Electrocardiography (ECG) is a sensitive method to detect early cardiac abnormalities. To observe relationship between serum ferritin and corrected QT interval (QTc).

Materials and methods: This Hospital based cross-sectional study was done in Chittagong Medical College Hospital (CMCH) on 96 Transfusion-Dependent Thalassemic (TDT) children during a period of twelve months. The study included clinical evaluation, haematological test and ECG.

Results: Out of 96 TDT patients, Hemoglobin E Beta were 63(65.6%), Beta thalassemia major were 33(34.4%) and 64(66.7%) were male whereas 32(33.3%) were female with a ratio of 2:1. Mean age of the patients was 10 years, mean duration of illness was 8.54 years, and mean frequency of transfusion was 14.41 times per year. In this study 41(42.7%) patients had serum ferritin < 2500 ng/ml, 32(33.3%) had serum ferritin between 2500 to 5000 ng/ml, and 23(24%) had more than 5000ng/ml. Mean ± SD of serum ferritin was found 3885.53 ± 3106.93. Mean QTc was found higher (447.70 ± 23.63) in the patients with serum ferritin more than 5000 ng/ml, followed by (446.38 ± 16.48) in 2500-5000 ng/ml and (428.49 ± 21.19) in the patients with less than 2500 ng/ml. Correlation between serum ferritin and QT and QTc was (r=0.415) and (r=0.365) respectively.

Conclusions: Significant positive correlation was found between serum ferritin level and QTc.

Key words: Thalassaemia, Serum ferritin, Corrected QT interval (QTc).

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Date of Submission : 11-02-2020
Date of Acceptance : 16-05-2020

INTRODUCTION

Worldwide thalassaemias are the commonest autosomal recessive disorders[1]. Prevalence of both beta thalassemia trait and Hb E trait is much high and expected annual cases are 1040 and 6443 respectively[2]. Among these patients, repeated blood transfusions causing chronic iron overload leads to variety of cardiac arrhythmias and sudden death[3]. So it is essential to predict and prevent complications by evaluating iron load. But the tools for estimating iron load like serum ferritin or cardiac MRI[4,5] is expensive for the poor patients and unavailable in the remote area of our country. Interestingly electrical abnormalities are the earliest manifestation of cardiac complications[6]. So ECG may be a very much cheap, available, non invasive and sensitive method to detect early cardiac abnormalities with sufficient accuracy. Prolongation of QT interval predicts increased risk of life threatening arrhythmias and sudden death[7]. But unfortunately it has not received sufficient recognition in the

literature. The study was aimed to evaluate QTc parameters and their relation with iron load which was likely to guide us to assume iron overload by a simple tool like ECG, in the remotest area where serum ferritin level or MRI is not possible.

MATERIALS AND METHODS

This cross-sectional study was conducted on patients of Thalassaemia confirmed with Hb -electrophoresis admitted to Paediatric ward, Chittagong Medical College Hospital (CMCH) Chattogram for over the period from 1 January 2016 to 31 December 2016. A total of 96 Transfusion-dependant Thalassemic child with Serum ferritin ≥ 1000ng/ml and aged 3 years to 18 years of both sex were enrolled consecutively in this study. Almost all the children were on convenient blood transfusion therapy without any history of iron chelation. Children with cardiac diseases like congenital or acquired heart diseases, heart failure, rheumatic diseases, acute ill patients with signs of infection, patients on antibiotics, on antihistamines or on anti-arrhythmic drugs and guardians didn't provide consent were excluded. From all eligible subjects after getting consent, clinical history was taken and all documents regarding disease were checked. Five (5) cc venous blood was collected and sent for estimation of level of serum ferritin. Estimation was carried out by Automated Chemiluminescence Immunoassay (CLIA) analyser. Patient's were arbitrarily divided into groups I, II & III according to ferritin level < 2500 ng/ml, 2500-5000 ng/ml and > 5000ng/ml. All subjects were performed electrocardiography in the Department of Cardiology in CMCH. Electrocardiography was performed using 12 lead ECG machine HP-1300 PLUS (Heart Care, China). ECG was checked by cardiologist who was unaware of the study. QT, QTc intervals were taken from ECG tracing produced by the electrocardiography machine automatically. QT intervals were measured from the onset of QRS complex to the end of T wave on the isoelectric line.

Ethical Committee approval was duly obtained from the Institutional Review Board of Chittagong Medical College Hospital, Chattogram prior to commencement of the study. The data were analyzed by using SPSS for windows 20 (IL,USA). Mean difference of different ECG parameters were tested between two groups of different Ferritin level by student's t test. The correlation between serum Ferritin and different QTc were measured by Pearson's correlation coefficient. p value <0.05 was considered statistically significant with a confidence interval of 95% level.

RESULTS

Out of 96 transfusion dependent thalassemic patients, 64(66.7%) were male whereas 32(33.3%) were female with a ratio of 2:1. Mean age of the patients was 10 years, mean duration of illness was 8.54 years, and mean frequency of transfusion was 14.41 times per year. In this study 41(42.7%) patients had serum ferritin < 2500 ng/ml, 32(33.3%) had serum ferritin between 2500 to 5000 ng/ml, and 23(24%) had more than 5000ng/ml. Mean ± SD of serum ferritin was found 3885.53 ± 3106.93. Among study populations, 27(28.1%) had prolonged QTc interval (Table I). Mean QTc was found higher (447.70 ± 23.63) in the patients with serum ferritin more than 5000 ng/ml, followed by (446.38 ± 16.48) in 2500-5000 ng/ml and (428.49 ± 21.19) in the patients with less than 2500 ng/ml (Table II). Correlation between serum ferritin and QT and QTc was (r=0.415, p<0.000) and (r=0.365, p<0.000) respectively (Table III). Significant positive correlation was found between serum ferritin level and QTc whereas no significant correlation was found between serum ferritin and other ECG measurements. Increment of QTc was found to be associated with increment of serum ferritin.

Table I : Distribution of corrected QT interval status among the study subjects (n = 96).

QTc Status	Frequency	Percentage (%)
Normal	69	71.9
Prolonged	27	28.1
Total	96	100.0

Table II : Comparison of QT and QTc intervals with different Ferritin levels among the study subjects.

	Ferritin Status				
	Group I (n = 41) Mean ± SD	Group II (n = 32) Mean ± SD	Group III (n = 23) Mean ± SD	p1*	p2**
QT Interval	316.90 ± 30.69	337.81 ± 30.36	356.52 ± 33.67	0.005 HS	0.000 HS
QTc Interval	428.49 ± 21.19	446.38 ± 16.48	447.70 ± 23.63	0.000 HS	0.001 HS

● Independent samples t-test significance:
* p1 = Group II compared with Group I, ** p2 = Group III compared with Group I.
Table showing that QT and QTc interval were significantly increased in group 2 (p=0.005, p=0.000) and group 3 (p=0.000, p=0.001) compared to group 1.

Table III : Pearson's correlation between serum Ferritin and various QT and QTc measurements (n = 96).

Correlation Between	Correlation Coefficient (r)	Significance
Serum Ferritin and QT Interval	+ 0.415	p = 0.000 Highly Significant
Serum Ferritin and Corrected QT Interval (QTc)	+ 0.365	p = 0.000 Highly Significant

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DISCUSSION

The present study was done in a Tertiary Care Hospital of Chittagong on 96 cases of transfusion dependent thalassemic patients from 1st January 2016 to 31st December 2016.Out of 96, Hb E-ß thalassemia was 63 (65.6%) and beta thalassemia major was 33 (34.4%) which is similar to other studies done in Bangladesh[8,9] . Male to female ratio was 2:1 in this study which nearly corresponds with other different studies[9].

Among the 96 patients, mean age was 10 years, mean duration of illness from diagnosis was 8.54 years. Mean serum ferritin was found 3885.53 ± 3106.93 with a median of 2820.00 ng/ml. 41(42.7%) patients had serum ferritin < 2500 ng/ml, 32(33.3%) had serum ferritin between 2500 to 5000 ng/ml and 23(24%) had more than 5000ng/ml. By taking repeated transfusion most of the children were maintaining their health, so the mean serum ferritin of our subjects was higher than that recorded in other studies. Cario et al found that 76/102 patients (75%) younger than 10 years had serum ferritin less than 1800 ng/ml[10,11]. The high mean serum ferritin of our study sample may be due to not taking chelation therapy by many and a non affordability of infusion pumps.

In this study, majority of the patients 60(62.5%) had transfusion 12 times per year and 25(26%) patients were with history of more than 12 times per year and showed that the more was the frequency of transfusion, the more was the serum ferritin level (3963.95 ± 3232.18 vs 4500.64 ± 3182.44 mg/ml). Study by Ikram N et al also found mean serum ferritin levels 3396 ng/ml with gradual increase in frequency of blood transfusion with age[12]. Similar results were also reported by others [13,14].

Durongpisitkul et al determined different variables and showed that in asymptomatic transfusion dependant thalassemic children, ECG should be used for screening patients for the detection of cardiac involvement[15]. In this study, 27(28.1%) of thalassemic patients had prolonged QTc interval. The mean serum ferritin of present study subjects was higher than that recorded in other studies and that may be the possible reason for prolonged QTc interval in our population[10,11].

Regarding the groups of 96 patients according to ferritin level, QT and QTc were all significantly increased in Group II (p=0.005 and p=0.000) and Group III (p=0.000 and p=0.001) when compared with Group I. There was no significant difference in other parameters of ECG leads among the three groups (p>0.05). In the present study significant positive correlation was found between serum ferritin and both QT (r=0.415, p<0.000) and QTc (r=0.365, p<0.000) respectively.

Mehmet et al also demonstrated that QT, QTc, were signi cantly prolonged in patients with β-thalassemia compared to healthy subjects (p<0.001)[3]. Study by Jon et al showed prolonged QTc significantly greater in patients having cardiac iron[16].

Study by Armen et al and Vincenjo et al showed the means of QT and QTc had significant differences between the case and the control groups[17,18]. Krzysztof et al concluded that serum ferritin affects the QT interval in a variety of medical conditions, possibly contributing to the emergence of fatal cardiac arrhythmias[19]. Mohammad et al Behzad et al and Amna et al concluded that ECG is an inexpensive, non-invasive test that has potential in the cardiac assessment of patients with -thalassaemia, particularly in resource-poor countries which favours our study[20-22].

LIMITATION

This was a single center study with smaller sample size. Metabolic markers causing QTc prolongation, were not considered in this study impart the most important limitation.

CONCLUSIONS

This study revealed a significant positive correlation between serum ferritin and QT parameters. So ECG may be useful for monitoring iron overload in thalassemic patients in countries like Bangladesh where the tests are not regularly affordable.

RECOMMENDATION

As the findings of this study are encouraging, it is important to expand the study. Further multicenter studies with nationally representative sample would be necessary to further support this parameter to be implemented in our clinical practice.

ACKNOWLEDGEMENT

The authors thank all the respected cardiologists, Lab technicians of Cardiology Department of Chattogram Medical College and physicians of the respected wards for contributing to carry out the research work.

DISCLOSURE

All the authors declared no conflict of interest.

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