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Original Research Article

To Study Early Cardiac Involvement in Transfusion Dependent Thalassemia Patients- A Comparative Prospective Study

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Abstract

Background: Beta thalassemia is a congenital haemolytic anaemia caused by reduced or absent synthesis of beta globin (haemoglobin subunit beta chain).Due to RBCs dysfunction, bone marrow expansion occurs and these patients require regular blood transfusion which lead to cardiac, pulmonary and hepatic complications due to increased serum iron load. This predisposes them for electrophysiological heterogeneity, which may provide substrate for triggered and re- entry activity and may be involved in genesis of arrhythmia and cardiac failure in beta thalassemia patients.

Introduction: Atrial fibrillation, atrial flutter, and intra-atrial re-entrant tachycardia are the most common clinically relevant rhythm disturbances in beta thalassemia patients. Constant and progressive cardiac impairment leads to irreversible cardiac failure which remains the major cause of death for these patients.

Objective: To study early cardiac involvement in transfusion dependent thalassemia patients.

Method: Cardiac autonomic function test for assessing sympathetic and parasympathetic control will be done by CANWIN-504(Cardiac Autonomic Neuropathy Analyser).

Conclusion: Hence the present study will be conducted to find out possible risk of cardiac involvement among beta thalassemia patients.

Keywords: Thalassemia, Transfusion, Cardiac Autonomic Neuropathy, Cardiac Impairment.

Introduction

Betathalassemia is a congenital hemolytic anemia caused by reduced or absent synthesis of beta globin (hemoglobin subunit beta chain). [1] The severity of clinical features depends on the destructed globin and the structural changes in other chains and the co-inheritance of the abnormal globin chains.

Due to dysfunction of red blood cells, the blood production in the bone marrow of these people increases, causing the bones to become deformed in the long run, especially the broad bones. [2] The patients also require regular blood transfusions, which causes the patients to develop complications such as increased iron levels in various organs. Early assessment of patients at a higher risk of cardiac arrhythmias is considered as one of the most important therapeutic goals [3]. The primary factor of cardiac damage in beta-thalassemia patients is iron overload. When the iron transfer capacities of transferrin are exceeded, non-transferrin bound iron appears in blood, which gets immediately buffered by cytosolic ferritin, degraded to haemosidrin, and stored in lysosomes When intracystolic buffering mechanism fail, toxic labile iron levels rise in cardiac myocyte ,resulting in oxidative damage to cell membrane and ion channels. This leads to (a)-decreased rapid phase 0 depolarization (b)-blockade of ryanodine calcium channels and oxidative stress mediated change in sarcoplasmic calcium release and uptake. This electrophysiological heterogeneity, may provide substrate for triggered and re-entry activity and may be involved in genesis of arrhythmia and cardiac failure in beta-thalassemia patients. [4,5,6]

Myocardial siderosis is known as major cause of death in beta thalassemia patients since it can lead to iron overload cardiomyopathy. Although this condition can be prevented if timely, effective

intense chelation is given to patients, the mortality rate of iron overload cardiomyopathy still remains high due to late detection of disease [7]. An association between CANS (Cardiac Autonomic Nervous System) findings and cardiac diseases risks has been confirmed in beta-thalassemia patients. However some studies have been conducted on CMR (Cardiac Magnetic Resonance) but very few studies have been done on CANS (Cardiac Autonomic Neuropathy System), hence we plan to conduct this study [7]. Atrial fibrillation, atrial is, intra atrial re-entrant tachycardia are the most common clinically relevant rhythm disturbance in beta- thalassemia patients [8].

In view of cardiac complications, serum ferritin concentration has been shown to correlate poorly with all stages of cardiac dysfunction. Accurate assessment of cardiac dysfunction are currently based on imaging techniques.8The prevention of cardiac death in beta thalassemia patients has indicated a role for CANS(Cardiac Autonomic Neuropathy System) in assessing cardiac dysfunction using ECG of R-R interval and autonomic BP measurement to identify beta-thalassemia patients at a higher risk of cardiac disease. [9]

Aims and Objective: Whether early detection of cardiac involvement can be studied by using CANS (Cardiac Autonomic Neuropathy System) in beta-thalassemia patients? This study was conducted for detecting early cardiac involvement in transfusion dependent thalassemia patients

Material and Method

Study design: A comparative prospective study was carried out at Department of Physiology of Bhagat Phool Singh Government Medical College, Khanpur Kalan, Sonepat, and Haryana after approval of protocol by institutional ethical committee.

Study population: Sample size based on preparation taking prevalence of cardiac diseases in beta- thalassemia patients as 0.8%with precision 2% and 95%CI with a population size of 50 at tertiary care hospital where study was conducted, the required sample was 48.The study was include 48 patients having age in between 6month and 19 years who were diagnosed with beta thalassemia. This was matched accordingly to age and gender with normal healthy population.

Study conduct: For each patient a data collection form was filled which included gender, age, age at which patient diagnosed with beta thalassemia, transfusion frequency, haemoglobin level, haematocrit, serum ferritin levels, LFT and lipid profile, Time interval between transfusion and CAN was recorded in the checklist. Autonomic nervous control can be noninvasively studied with cardiovascular reflex test, such as the Valsalva maneuver, the orthostatic test, the isometric test and by measuring heart rate variability.

Cardiac autonomic function test for assessing early cardiac involvement (sympathetic and parasympathetic control) was done byCANWIN-504(Cardiac Autonomic Neuropathy Analyser).

Inclusion criteria: All the patients diagnosed with beta- thalassemia based on the high performance liquid chromatography (HPLC) test were included in this study. For all the patients visiting day care transfusion at the hospital, written informed consent will be obtained from parentsorlegalguardianifpatientislessthan12yearsof age and informed consent will be taken from the patient above 12 years of age.

Exclusion criteria: Patients with known cardiac disease, thromboembolic events, diabetes mellitus, sickle cell anemia, history of fever or use of sedatives in last 24 hours and any acute illness in last two weeks were excluded from the study.

Intervention -CANWIN504 (Cardiac Autonomic Neuropathy Analyser): Canwin is the state of art window-based computer having cardiac autonomic neuropathy) analysis system with interpretation It has an extensive data base to keep track of subject history and for archive test retrieval and comparisons. Being fully automatic, the need of manual recordings, readings and calculation is subjected. Inbuilt time domain waveform analysis and blood pressure measurements make the task of conducting all the autonomic nervous systems tests very easy. Cardiac Autonomic Neuropathy Analyser model CANS-504 is important tool to measure and diagnose autonomic dysfunctions using ECG of R-R interval and autonomic BP measurement.

CANWIN-504

Figure 1:

For checking autonomic dysfunction, 2 types of tests will be done -

a) Tests for assessing sympathetic activity –

Isometric hand grip exercise test: Before the exercise, subjects were allowed to rest for 20minutesina quiet room. Resting blood pressure of all subjects was measured by auscultatory method with the help of sphygmomanometer .First kortkoff sound indicates systolic blood pressure and fifth kortkoff sound indicates diastolic blood pressure. Isometric hand grip test was done in both study and control groups. After recording basal blood pressure, subjects were asked to perform isometric hand grip exercise. Subjects were told to hold the handgrip spring dynamometer in dominant hand to have full grip. Handlers of dynamometer were compressed by subjects with maximum efforts for few seconds. Then subject were told to perform 30 %of maximum hand grip for 3 minutes. During the test BP was recorded from non-exercising arm and again recorded after 5min of exercise.

b) Tests for assessing parasympathetic activity Resting heart rate: was calculated from ECG using standard limb leads

i) Heart rate response to standing (30:15)-was calculated as ratio between R-R interval at beats30and15 of the ECG recorded immediately upon standing. This test evaluates the cardiovascular response elicited by change from horizontal to vertical position. The typical heart rate response to standing is largely attenuated by parasympathetic blockade.

ii) Heart rate response to deep breathing –

Heart rate was recorded first during normal breathing at rest and then during breathing (6/min) ECG, 3rd and 6th respiration minimum R-R interval and corresponding heart rate was calculated.

Observations and Results

The collected data was entered in Excel spreadsheet. Mean±SD calculated for quantitative data, percentage Student t-test was used for normally distributed variables to find the mean difference using Statistical Package for the Social Sciences software. P-value <0.005 considered as statistically significant.

Table 1: Distribution of Mean and Standard Deviation among control and case group for sympathetic tests.

Sympathetic test	Control(24) Mean±SD	Case(24) Mean±SD
Sustained Hand grip (Change in diastolic BP)	76.71±8.483	71.13±5.937

Table1: Shows that– The mean score of Sustained hand grip in case group (71.13±5.937) is lower than control group (76.71±8.483), but the difference is found to statistically insignificant.

Table 2: Distribution of Mean and Standard deviation among control and case group for parasympathetic tests

Case(24) Mean±SD	Parasympathetic test	Control(24) Mean±SD
88.88±12.959	Resting Heart Rate(bpm)	84.08±17.675
96.96±62.116	Deep breathing	162.96±80.373
86.92±49.761	Standing30:15	135.21±60.935

Table 2 shows that–

- Mean score of resting heart rate in case group (88.88±12.959) is higher than control group (84.08±17.675); but the difference is found to be statistically insignificant.
- Means score of Deep breathing in case group (96.96±62.116) is lower than control group (163.96±80.373).Mean score of Standing Blood pressure is lower in case group (86.92±49.761) than control group (135.21±60.935).

Table 3: shows mean difference among case and control group in sympathetic test.

Sympathetic test	Control (24) Mean±SD	Case(24) Mean±SD	t-value	p-value
Sustained hand grip (change in diastolic BP)	76.71±8.483	71.13±5.937	2.642	0.11

Table 3: shows that- The mean difference in isometric hand grip between control and case group was statistically insignificant. (P>0.005)

Table 4: shows mean difference among case and control group in parasympathetic tests

Parasympathetic test	Control(24) Mean±SD	Case(24) Mean±SD	t- value	p- value
Resting heart rate (bpm)	84.08±17.675	88.88±12.959	1.080	0.286
Deep breathing	162.96±80.373	96.96±62.116	3.183	0.003
Standing 30:15	135.21±60.935	86.92±49.761	3.007	0.004

Table 4: shows that-

- The mean difference in Resting heart rate among control and case group is statistically insignificant (P>0.005)
- The mean difference in Deep breathing among control and case group is statically significant (P<0.005).
- The mean difference in Standing Blood pressure among control and case group is statically significant (P<0.005).

Discussion

In the present study, the response of autonomic activity (sympathetic and parasympathetic) in transfusion dependent thalassemia patients was studied and compared with controls group (non-statistically significant) is observed for deep breathing and standing 30:15. transfusion dependent thalassemia patients). The study was carried out at Bhagat Phool Singh Government Medical College, Sonepat in Department of Physiological on the sample size of 48(24 controls +24 transfusion dependent thalassemia).The tests for sympathetic and parasympathetic involvement are performed. The early parasympathetic involvement (p<0.05) was observed in transfusion dependent thalassemia patients.

These results were consistent with studies done by other researchers on transfusion dependent thalassemia patients. The results are in accordance with study done by Sneha Bhatkar and Surendra Shivalkar. Decrease in Deep breathing difference is probably mainly due to decreased vagal tone indicating abnormal parasympathetic function in beta thalassemia major patients.30:15 is used commonly to assess the damage of afferent or efferent limb of cardiovascular reflexes. Although both sympathetic and parasympathetic fibres participate in the changes of R-R intervals after this procedure, this test is mainly used to assess the integrity of parasympathetic fibres participating in the autonomic control of heart. Decreased 30:15 ratio may be due to decreased parasympathetic activity [10].

The results were consistent with study done by Kamol Chandra Das and Sultana Ferdousi. In patients with thalassemia cardiac output is increased as they suffer from chronic anaemia which is attributed to increased cardiac damage and heart rate. Moreover, expanded blood volume at the time of blood transfusion may cause uncontrolled stimulation of cardiac receptors with sympathetic afferents and vagal withdrawal and consequently impaired cardiac tone. Though cardiac output is increased but due to low peripheral resistance, blood pressure is decreased in these patients. [11]

Another study by V. Russo also satisfies our results. beta thalassemia major population show an increased QRS duration and QRS fragmentation, which correlate with myocardial iron overload

associated with MRIT2*(T2- star magnetic resonance) compared with healthy controls, supporting that myocardial iron overload cause abnormal and non-homogeneity repolarization which may be responsible for electrocardiogram abnormalities [5].

Another study by Sukardi R Wahidiyat satisfies our results. Reduced deceleration capacity means reduced vagal excitation, which corresponds down regulation and increases sudden cardiac death risk6.Thalassemic patients carrying typical systolic function and iron overload, abnormal left ventricular relaxation time, represented as prolonged isovolumetric relaxation time which is the first symptom of diastolic dysfunction [13]. Cardiac involvement is the most important cause for mortality and morbidity in young beta thalassemia patients who have not been treated [14].

Diastolic BP following isometric hand grip test didn't show any statistically significant (P>0.05) change in transfusion dependent thalassemia patients when compared with control (non-transfusion dependent thalassemia patients).The patients were also not able to perform isometric hand grip test as per the desired. These results are not in accordance with study done by Franco Vegio on BP and HR in young thalassemia major patients. The study suggested for the suppression of sympathetic activity, is a normal mechanism to control BP increased after blood transfusion in transfusion dependent thalassemia patients [12].

However the study done by M Cetin doesn't correlate with our results. This result signifies no statistically significant difference between TT group and control group in terms of Standard deviation of all mean R-R intervals, Standard deviation of the mean normal-normal R-R intervals, Route means square of the successive differences values. Further studies are needed to assess for prognostic significant findings and the role of cardiac volume mechanoreceptors in heart rate and BP control [9].

More studies are required about this subject as intense chelation therapy fails to control the rate of iron overload and cardiomyopathy. Slow Breathing Exercises could be advised to increase parasympathetic activity in transfusion dependent patients of thalassemia.

Summary

The present study was aimed to study early cardiac involvement in transfusion dependent thalassemia patients and compare it with non-thalassemia patients. The study was conducted on 23 transfusion dependent thalassemia patients and 24 controls (non thalassemia patients). Tests are performed to study early sympathetic and parasympathetic n in transfusion dependent thalassemia patients. Isometric hand grip test was used for assessment of sympathetic activity. To assess parasympathetic activity Resting heart rate, heart rate response to deep breathing and standing 30:15 was recorded. In our study it was found that there was a significant change to deep breathing and standing BP among the case as well as control group reflecting higher parasympathetic activity while test for sympathetic system has not shown significant difference among both groups .The present study showed the role of parasympathetic activity in controlling hemodynamic in transfusion dependent thalassemia patients to prevent cardiac arrhythmia due to electrophysiological heterogeneity following cardiac overload.

Conclusion

In our study it was concluded that early parasympathetic involvement is observed in transfusion dependent thalassemia patients. The electrophysiological heterogeneity, may provide substrate for triggered and re – entry activity and may be involved in genesis of arrhythmias and cardiac failure in beta thalassemia patients. Sympathetic involvement is not recognized and the desired age group was not capable to perform the isometric hand grip test properly as per the desired. Slow Breathing Exercises could be advised to increase parasympathetic activity in transfusion dependent thalassemia patients. More studies are required about this subject as intense chelation therapy fails to control the rate of iron overload and cardiomyopathy.

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