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Heart Rate Variability Analysis in Beta Thalassemia Major Patients Receiving Different Therapeutic Aids

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ABSTRACT

The purpose of this study was to evaluate heart rate variability(HRV) in beta(β) thalassemia major(TM) patients receiving different therapeutic aids in a hospital based comparative observational study. A total of 56 confirmed beta thalassemia major patients in the age range 5-20 years ,taken from the day care center of S.M.S.Medical College,Hospital,Jaipur were examined and the grouping was done on the basis of receiving of regular/irregular blood transfusion along with regular/irregular or no iron chelation therapy.They had no symptoms and signs of cardiovascular disease as assessed clinically ,routine laboratory profile and echocardiography. All patients underwent recording of impedance peripheral pulse in the right forearm for five minutes. All frequency and time domain HRV parameters were found to be significantly reduced in patients receiving irregular/no iron chelation therapy along with regular/irregular blood transfusion. Therefore TM patients should receive regular iron chelation therapy along with regular blood transfusion so as to prevent/delay iron overload which may influence cardiac autonomic balance.

Keywords: Heart rate variability, thalassemia major,iron chelation therapy, blood transfusion.

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INTRODUCTION

Beta (β) Thalassemia is an inherited disorder of hemoglobin synthesis of β chain of globin molecule resulting in chronic hemolytic anemia and requiring lifelong blood transfusion therapy for survival [1].

Cardiac complications represent the leading cause of mortality in patients of thalassemia major [2]. Cardiac involvement in thalassemia patients is generally characterized by iron induced ventricular dysfunctions leading to heart failure [3-5] Before the introduction of iron chelation therapy iron overload from transfusions was a frequent cause of morbidity & mortality in thalassemia patients [6].Death was often due to cardiac failure which typically began before the patient reached 20 years of age. Iron chelation therapy begun early in life prolongs survival without cardiac disease [7].

Heart rate variability is a noninvasive electrocardiographic marker reflecting the activity of sympathetic & vagal components on the sinus node of the heart. In a normal heart with an integer ANS, there will be continuous physiological variations of the sinus cycles reflecting a balanced sympathovagal state & a normal HRV [8]. In a damaged heart, the changes in the activity of afferent & efferent fibers of ANS & in the local neural regulation will contribute to the resulting sympathovagal imbalance reflected by a diminished HRV.

In high risk patients, a persistent sympathetic activation & a reduced vagal tone may determine a marked reduction in dynamic complexity of heart rate fluctuations that would make heart period less adaptable & less able to cope up with the requirements of a continuously changing environment [9, 10].

MATERIAL AND METHODS

A total of 56 β thalassemia major patients, age ranging between 5-20 yrs. of both sexes were recruited from thalassemia day care center of S.M.S. Hospital, Jaipur. They were divided into four (age & sex matched) groups(T1,T2,T3,T4) depending upon receiving of blood transfusion & iron chelation therapy. The study was performed on the day prior to receiving of blood transfusion. Written informed consent was obtained from parents of all patients & patients above 18 yrs of age. The inclusion criteria for patient selection were, confirmed TM patients receiving blood transfusion. Exclusion criteria were, patients having any acute or chronic illness, patients receiving medication which may affect autonomic functions and patients having symptoms and signs of heart disease as assessed clinically, by routine laboratory profile and echocardiography.

- Group T1- patients receiving regular blood transfusion and regular iron chelation therapy.
- Group T2-patients receiving regular blood transfusion and irregular iron chelation therapy.
- Group T3- patients receiving regular blood transfusion and no iron chelation therapy.

- Group T4- patients receiving irregular blood transfusion and no iron chelation therapy.
- The study was approved by the institutional ethical committee.

Heart rate Variability measurement

Impedance peripheral pulse in the right forearm was recorded in the supine posture for 5 minutes after 5 minutes of supine rest in a quiet environment at a room ambient temperature of 24-25^{0}C,breathing quietly with eyes closed. The detection of impedance peripheral pulse was digitally done by Medical Analyzer, Non Invasive Vascular Monitor,(Nivomon).

The frequency domain parameters of HRV viz Total Power(TP),High frequency(HF) Power, Low frequency(LF)Power, Low frequency normalized units(Lfnu),High frequency normalized units(HFnu) were analyzed using fast Fourier Transform(FFT) (Task Force, 1996) [11]. The time domain parameters used in the analysis of HRV were SDNN, RMSSD, and PNN50.

SDNN -Standard deviation of R-R intervals over the selected time interval.
RMSSD – Square root of mean of sum of the squares of differences between adjacent R-R intervals
PNN50 – Percentage of NN50 count of all R-R intervals

All parameters are presented as mean±SD. A "p" value less than 0.05 was considered statistically significant.

Statistical analysis : Numerical data are expressed as Mean±S.D. Stastical analysis was performed using Microsoft excel software 2003 and inter group comparison was done by one way Anova.

RESULTS

Total power, low frequency &high frequency power in absolute terms decreased from group T1 to group T4.High frequency power in normalized units also decreased from group T1 to group T4.Low frequency power in normalized units & LF/HF ratio, a marker of sympathovagal balance were increased from group T1 to group T4 **.**The time domain parameters viz SDNN, RMSSD, PNN50 also decreased from group T1 to T4(Table I).Comparison of various frequency & time domain parameters between various groups of thalassemia patients showed highly significant 'p' values(<0.001).However LF power showed a significant 'p'value (0.0015)(Table II).

DISCUSSION

The reduced HRV expression in β thalassemia major patients who were receiving inadequate /no iron chelation therapy could be interpreted as evidence of early cardiac autonomic neuropathy in young β thalassemia major patients.

The Total power and SDNN are indicators of both sympathetic &parasympathetic activity. The HF Power, RMSSD and PNN50 values are reliable indicators of parasympathetic activity.LF Power &LF/HF ratio provide an adequate reflection of sympathetic activity. Reduced HRV which reflects both sympathetic &parasympathetic activity predict increased risk for subsequent cardiac events.

The reduced HRV expression &impaired sympathovagal activity may be explained by chronic anemia which leads to a persistent sinus tachycardia &a sustained decrease in autonomic fluctuations.

It is evident from our observations that patients who received inadequate or no iron chelation therapy, had more reduced HRV parameters which supports the explanation that deposition of iron in cardiac myocytes &myocardial fibrosis may cause heterogeneous ventricular depolarization & could lead to abnormal excitability of iron loaded heart cells [12].

It has been reported that iron reduces the number of functional cardiac sodium channels &enhances the inactivated state of functional channels causing reduction in overshoot of cardiac action potential in iron loaded cardiac myocytes [13].Iron has been reported to produce peroxidative damage to DNA [14] and also damages membrane lipids & proteins [15,16].In cultured rat cardiomyocytes invitro treatment with iron altered membrane fatty acids &suppressed mitochondrial respiratory enzymes with a concomitant reduction in cellular ATP [17,18].The decrease in ATP might alter phosphorylation of Sodium channel protein which affects steady state inactivation & recovery from inactivation [19, 20]

An increase in the cellular iron content is also believed to drive an increase in the formation of OH^- radical, a highly reactive oxygen species (ROS) from H_2O_2 which is suggested to be the main cause of damage associated with iron overload [21]. This is also thought to be one of the main mechanism by which iron overload leads to heart impairment [22,23].

Thus chronic iron overload may lead to development of cardiomyopathy manifested by ventricular arrhythmias & heart failure. Iron loaded cardiomyocytes may have an abnormal excitability reflected as altered HRV as evidenced by this study. Thus our observations indicate that reduced HRV parameters which reflect impaired activity of both sympathetic & parasympathetic nervous system, predict increased risk for subsequent cardiac events in young β thalassemia major patients. The deposition of iron in cardiac myocytes leading to cardiac autonomic dysfunction can result into sudden appearance of arrhythmias &may prove fatal.

CONCLUSION

Regular iron chelation therapy in young β thalassemia major patients predicts a better outcome. Quantification of myocardial iron content using magnetic resonance imaging is costly & not widely available. Therefore all β Thalassemia major patients should be screened for cardiac autonomic dysfunctions using heart rate variability analysis to detect cardiac complication in the pre-clinical stage of cardiac involvement.

Table No. I: Comparison of mean ±SD of various parameters of HRV in various groups of β Thalassemia major patients

S.N	Parameter	Group T1	GROUP T2	Group T3	Group T4
1	TP(ms^2)	3419.43±1744.22	1324.18±1289.46	709.746±11.84	301.06±186.25
2	LF Power(ms^2)	456.67±169.38	390.81±369.67	229.32±263.35	91.95±61.17
3	HF Power(ms^2)	1269.55±797.92	451.06±449.74	141.54±164.04	30.88±24.01
4	LFnu(%)	28.21±4.70	48.15±4.73	62.09±1.94	74.62±6.10
5	HFnu(%)	71.79±4.70	51.85±4.73	37.91±1.94	25.38±6.09
6	LF/HF ratio	0.40±0.09	0.94±0.18	1.64±0.14	3.20±1.11
7	SDNN(ms)	0.09±0.02	0.05±0.02	0.04±0.01	0.03±0.008
8	RMSSD(ms)	0.11±0.04	0.06±0.03	0.05±0.02	0.03±0.008
9	PNN50 (%)	0.25±0.17	0.07±0.06	0.07±0.04	0.04±0.05

Table No.II: Comparison of various parameters of HRV between various groups of Thalassemia patients by ANOVA

S.No	Parameter	Source of variation	SS(sum of squares)	Df(degree of freedom)	MS(Mean square)	F value	p value	Significance
1	Total Power(ms^2)	Between groups	80668148	3	26889383	19.52958	<0.001	HS
		Within groups	71596431	52	1376854			
2	LF Power(ms^2)	Between groups	1131573	3	377190.9	5.87575	0.0015	SIG
		Within groups	3338115	52	64194.51			
3	HF Power($ms^{2)}$	Between groups	13164300	3	4388100	18.81156	<0.001	HS
		Within groups	12129838	52	233266.1			
4	LF nu(%)	Between groups	16627.4	3	5542.467	241.1985	<0.001	HS
		Within groups	1194.901	52	22.97886			
5	HF nu(%)	Between groups	16627.4	3	5542.467	241.1985	<0.001	HS
		Within groups	1194.901	52	22.97886			
6	LF/HF ratio	Between groups	61.97811	3	20.65937	59.63899	<0.001	HS
		Within groups	18.01317	52	0.346407			
7	SDNN(ms)	Between groups	0.02672	3	0.008907	29.38983	<0.001	HS
		Within groups	0.015759	52	0.000903			
8	RMSSD(ms)	Between groups	0.062708	3	0.020903	26.75421	<0.001	HS
		Within groups	0.040627	52	0.000781			
9	PNN50(%)	Between groups	0.40277	3	0.134257	13.39769	<0.001	HS
		Within	0.521086	52	0.010021			

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