

Fibroscan Study in Relation to Liver Function Test in Cases of Hemoglobinopathies

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Abstract

Introduction: Hemoglobinopathies are the most common single gene disorders. Beta-thalassemia is one of the most common hemoglobinopathies worldwide, and a high prevalence is seen in Mediterranean region, central Asia, India, and Far East countries. Recurrent ischemic insults with parenchymal necrosis can result in hepatic fibrosis, chronic liver disease, and cirrhosis. Liver biopsy has historically been the primary means to evaluate for fibrosis and monitor disease progression, but it has significant limitations. Vibration controlled transient elastography (VCTE) utilizing fibroscan uses an ultrasound transducer probe to create an elastic shear wave through vibrations of mild amplitude and low frequency (50Hz) which are transmitted through liver tissue.

Material & Methods: Hospital based cross sectional study was conducted involving patients under 18 years of age registered for treatment of haemoglobinopathies in the Department of Pediatrics, of Rajendra Institute of Medical Sciences, Ranchi during June 2021 to June 2022.

Result: It was observed that AST, ALT & ALP showed some progressive increase with increase in stage of fibrosis. Higher incidence of liver fibrosis was observed as patients age advances.

Conclusion: Fibroscan is a recent technology which could detect the earliest changes in hepatic pathology without invasion, it is a painless technique and correlates well with changes in hepatic enzyme leading to identification of pathologic changes.

Key words: Fibro scan, Liver fibrosis, LFT.

Introduction

Hemoglobinopathies are the most common single gene disorders. There are several hundred

of these disorders though the thalassemys - alpha and beta and the sickling disorders make up the vast majority. Beta-thalassemia is one of the most common hemoglobinopathies worldwide, and a high

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prevalence is seen in Mediterranean region, central Asia, India, and Far East countries.¹ Beta-thalassemia major (TM) results in lifelong requirement of blood transfusion to survive. Long-term transfusion results in iron deposition in the parenchymal tissues of various organs, resulting in organ damage. The liver is the major site of iron and overload (IO), containing 70% or more of total body iron content.² Persistent IO as indicated by liver iron concentration (LIC) results in significant fibrosis and ultimately cirrhosis.³ Therefore, monitoring of LIC in TM patients is of utmost importance to prevent life-threatening complications.⁴

Sickle cell disease (SCD) or homozygous sickle cell anaemia is the most common inherited disorders of erythrocytes, characterized by the presence of pathogenic hemoglobin S(HBS).⁵

Recurrent ischemic insults with parenchymal necrosis can result in hepatic fibrosis, chronic liver disease, and cirrhosis.⁶ Liver biopsy has historically been the primary means to evaluate for fibrosis and monitor disease progression, but it has significant limitations. Liver biopsy is an invasive procedure that can result in significant complication.⁷ Accurate assessment of fibrosis stage is further limited by sampling error and inter-observer variation.^{8,9} Vibration controlled transient elastography (VCTE) utilizing fibroscan uses an ultrasound transducer probe to create an elastic shear wave through vibrations of mild amplitude and low frequency (50Hz) which are transmitted through liver tissue. The probe utilizes pulse echo ultrasound to follow the propagation of the shear wave to measure velocity(m/s) and provide a liver stiffness measurement (LSM) in a representative volume of liver tissue that is 100-fold greater than obtained by needle biopsy.^{10,11} With this background present study was conducted to assess status of liver using fibroscan and liver function test.

Material & Methods

Hospital based cross sectional study was conducted involving patients under 18 years of age registered for treatment of haemoglobinopathies in the Department of Pediatrics, of Rajendra Institute of Medical Sciences, Ranchi during June 2021 to June 2022.

Data was collected by using pretested & predesigned questionnaire. Detailed history of all study participants was taken followed by through

clinical examination, laboratory investigation and fibroscan study.

Sample size: Average 100 patients were registered for the treatment of hemoglobinopathies in one year. Among these 50 percent receive more than 20 transfusions. Considering this 50 patients receiving more than 20 transfusions were included in the study.

Inclusion criteria:

All hemoglobinopathies patients under 18 years of age and those who give informed consent for the study.

Exclusion Criteria:

1. Patients with any other liver pathology such as:
2. Hepatitis B (hepatitis B surface antigen [HBsAg] positive),
3. Hepatitis C (anti-hepatitis C virus [HCV] positive),
4. Human immunodeficiency virus (enzyme-linked immunosorbent assay [ELISA] positive),
5. Wilson's disease (ceruloplasmin <20 mg/dL and 24-hour urinary copper >100 mg),
6. Autoimmune hepatitis (positive for serum anti-nuclear antibody [ANA],
7. Anti-smooth muscle antibody [ASMA].

Purpose of the study was explained to the study participants and their parents. Only after written consent of parents, study participants were enrolled in the study. Institutional ethics committee permission was taken prior to beginning of the study. Confidentiality of the information was ensured.

Methodology and Laboratory Investigations:

Detailed history regarding duration and number of blood transfusions, history of drug intake, any other past illnesses was taken. The patient has to undergo Fibro scan study of liver a non-invasive method, liver function test (AST,ALT& ALP) and serum ferritin will be done in all the patients.

Fibro scan is performed with the patient lying supine, an ultrasound-like probe is placed on the skin over the liver area, typically in the right mid-axillary line. The patient has feeling of a "flick" each time a vibration wave is generated by the probe. Approximately it takes around 10 minutes to perform this test.

Collection of samples Sterile venipunctures were used to take blood samples. After centrifuging samples for ALT, AST, ALP, and ferritin for 20 min at a speed of 2000–3000 rpm, the samples were stored at –80 C until testing. Prior to giving packed red blood cell transfusions, all samples were collected. Abbott Architect ci4100 analyzer was used to measure LFT and serum ferritin.

The results of fibro scan study presented in kilopascals (kPa). Results interpretation:

1. Fibrosis score F0 to F1 indicates either no liver scarring or minimal liver scarring (2–7 kPa)
2. Fibrosis score F2: Moderate scarring of the liver (8–9 kPa)
3. Fibrosis score F3: Severe scarring of the liver (9–14 kPa)
4. Fibrosis score F4: Cirrhosis (advanced liver scarring) (14 kPa or higher)

The highest outcome is 75 kPa.

Statistical Analysis:

Data collected during the study compiled in Microsoft excel version 2019 and further analysis done using SPSS 25.0 software. Categorical data was expressed in proportion, and percentage and numerical will be expressed in mean and standard deviations (SD). Depending on type of data parametric and non-parametric test is applied to the test the level of significance. P-value less than 0.05 considered as significant.

Result

A total of 52 beta-thalassemia major patients with a mean age of 8.47 ± 3.48 years were enrolled in this study.

Table 1: Distribution of study participants as per Demographic details

Characteristics	Values
Age	8.47 ± 3.48
Gender	
Male	38 (73.1%)
Female	14 (26.9%)
Disease	
Beta Thalassemia Major	47 (90.4%)
Sickle cell anemia	05 (9.6%)

A total of 52 beta-thalassemia major and Sickle cell anemia patients with a mean age of 8.47 ± 3.48 years were enrolled in the study. Out of total study participants 38 (73.1) were male and 14 (26.9) were females.

Table 2: Comparison of study participants with and without fibrosis of liver

Parameters	No Fibrosis	Fibrosis	Value
Age (mean±SD)	5.9±3.6	9.8±2.5	<0.05
Gender			
Male	11(61.1%)	27(79.4%)	
Female	7(38.9%)	7(20.6%)	
AST	70±21	99±24	
ALT	74±22	120±40.3	
ALP	203±118	305±116	
No. of blood transfusion	43±19	126±51	
Serum Ferritin	1663±414	2823±901	

It was observed that AST, ALT & ALP levels are significantly higher in patients with fibrosis, male participants affected more compared to female participants, proportion of patients with fibrosis was significantly higher with no. of blood transfusion 126±51 and serum ferritin level 2823±901.

Table 3: Distribution of study participants as per stage of liver fibrosis

Stage of fibrosis	Beta Thal Major	Sickle cell anemia	Total
F0 & 1	14	4	18
F2	8	1	9
F3	12	0	12
F4	13	0	13

Fifty-two patients underwent TE and the proportions of patients having F0&F1, F2, F3 and F4 were 18, 9, 12 and 13. Thirty-four individuals had significant fibrosis, according to the classification (F2 and higher).

Table 4: Distribution of study participants as per mean AST, ALT & ALP in respective stage of fibrosis

Stage of fibrosis	Mean & SD	AST(U/L)	ALT(U/L)	ALP(U/L)
F0 & 1	Mean	70.78	74.06	203.17
	SD	21.17	22.75	118.76
F2	Mean	85.67	93.44	237.11
	SD	16.09	25.23	104.75
F3	Mean	86.42	105.58	297.92
	SD	14.32	25.11	108.73
F4	Mean	120.69	152.92	359.08
	SD	20.51	39.36	111.76

It was observed that AST, ALT & ALP showed some progressive increase with increase in stage of fibrosis.

No significant difference was observed between gender and mean of median stiffness.

Table 5: Distribution of study participants as per blood transfusion and mean of median stiffness

Range of blood transfusion	Mean of median stiffness
21-100	6.75
101-150	15.05
151-250	17.93

It was observed that as number of transfusion increases there is an increase in the severity of liver fibrosis suggesting that there is a strong positive correlation between the number of blood transfusions and median stiffness of liver.

Discussion

A total of 52 beta-thalassemia major and Sickle cell anemia patients with a mean age of 8.47 ± 3.48 years were enrolled in the study. Out of total study participants 38 (73.1) were male and 14 (26.9) were females. In the present study, 34 (65%) patients were deemed to have significant fibrosis (F2, F3, F4). Al-Khabori et al¹² reported significant fibrosis in 60% of patients.

Table 6: Distribution of study participants as per age & mean of median stiffness

Age in years	Mean of median stiffness
1-5	5.200
6-10	10.2000
11-15	16

Higher incidence of liver fibrosis was observed as patients age advances.

Present study revealed that level of AST, ALT & ALP in patients with fibrosis are on the higher side as compared to those without fibrosis. AST, ALT and ALP are the most common laboratory values that clinicians check when evaluating liver function. AST, ALT & ALP showed some progressive increase and was statistically significant in advanced liver disease. According to Ahmed et al¹³, scar tissue caused by fibrosis can obstruct or restrict blood flow within the liver, this can starve and ultimately kill healthy liver cells, leading to the formation of more scar tissue, which impairs liver function and allows enzymes from damaged tissue to leak. Present study revealed median stiffness of patients were positively correlated to ALT, AST & ALP. Rise in the level of AST, ALT & ALP was seen as the fibrosis progresses. Giovanna Ferraioli et al¹⁴ has found the similar correlation.

Table 7: Distribution of study participants as per gender & mean of median stiffness

Gender	N	Mean of median stiffness (kPa)	Standard Deviation
Male	38	10.86	5.7144
Female	14	10.69	8.9403

p= 0.1151

Not significant

It was observed that as number of transfusion increases there is an increase in the severity of liver fibrosis suggesting that there is a strong positive

correlation between the number of blood transfusions and median stiffness of liver. Similar result was seen in the study by Remacha et al¹⁵ the quantity of blood transfusions has a direct correlation with transfusion iron excess. Additionally, Tari et al.¹⁶ (2018) reported that receiving numerous blood transfusions might lead to iron excess, which further disrupts metabolism and damages tissue and organs.

Higher incidence of liver fibrosis was observed as patients age advances. This may be due to increased iron load brought on by exposure to additional blood transfusions. On the other hand, Al-Khabori et al¹² recorded that age had no bearing on the likelihood of substantial liver fibrosis developing. In present study there was no gender association with liver fibrosis. Contrarily, Al-Khabori et al¹² discovered a link between liver fibrosis and gender in TM patients.

Conclusion

Hepatic fibrosis is a common complication following repeated blood transfusion, there is a need to identify these changes early in patients in order to prevent or delay complications. One of the method to identify early defects in hepatic pathology is to estimate liver enzymes and other biochemical parameters including serum ferritin and liver biopsy, these method involves repeated invasive intervention which leads to inconvenience to the patient as well as family members and attendants. Fibroscan is a recent technology which could detect the earliest changes in hepatic pathology without invasion, it is a painless technique and correlates well with changes in hepatic enzyme leading to identification of pathologic changes.

Ethical Clearance: Approved by institutional ethical committee. **Name:** Institutional Ethical Committee, Rajendra Institute of Medical Sciences,

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Conflict of Interest Declaration': No conflict of interest

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