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Research Article

Virtual touch tissue quantification of liver in thalassemia

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ABSTRACT

Background: Objective of current study was to study the liver stiffness measurements in thalassemia patients by virtual touch tissue quantification technique.
Methods: Study was case control study. Study was conducted in Pediatrics department in a tertiary care teaching hospital, between Febrauary 2015 to June 2015. 32 thalassemia patients attending outpatient department or admitted for blood transfusion were included in the study. 32 nonthalassemic patients with normal liver function tests were selected by convenience as controls to detect normal liver stiffness value. Assessment of liver stiffness was done using Acoustic radiation force impulse elastography from Philips iu22 machine using low frequency C5-2probe. 10 measurements were taken from right lobe segment-5 of liver about 1 to 2 cm from skin surface, from the right intercostal window, with patient lying in supine position, with right arm abducted. Liver stiffness measurements were taken by the same person (radiologist) to minimize inter-observer variabilities. Serum ferritin was measured by particle induced immunoturbidimetric method in the biochemistry laboratory. Primary outcome was mean value of liver stiffness measurement in thalassemia patient and to know the effect of sex, age, serum ferritin and annual blood cell requirement on the Liver stiffness value.
Results: Mean value of liver stiffness value in thalassemia patients was 1.48 m/s and non-thalassemia patients were 1.15 m/s. Difference between Liver stiffness measurement between thalassemia cases and controls were significant with p value <0.001. Cut off value of 1.24 differentiates between the two groups with sensitivity of 93.8 % and specificity of 94%. Liver stiffness value is highly correlated with serum ferritin level ($r=0.517$, $p<0.002$). There were no statistically significant difference in Liver stiffness measurement between cases and controls with respect to age, sex, annual blood cell requirement.
Conclusions: Liver stiffness value is higher in patients with thalassmia and differs significantly from non thalassmic children.

Keywords: ARFI, Liver stiffness, Serum ferritin, Thalassemia

INTRODUCTION

Beta thalassemia is a hereditary hemoglobinopathy disorder requiring chronic blood transfusion. Frequent blood transfusion and increased gastrointestinal absorption of iron can lead to secondary iron overload.[1] Excess free iron mediates organ injury through lipid peroxidation of organelle membrane, increased lysosomal fragility and decreased mitochondrial oxidative metabolism. Liver is the primary site of iron storage and only site of synthesis of transferrin and ferritin.[2] Liver contains 70-80% of body iron stores. In thalassemia, abnormal liver functions are correlated with high ferritin levels and age at which transfusion was initiated. Hepatic siderosis, portal fibrosis and even cirrhosis may develop despite iron chelation therapy. Progression of liver fibrosis is largely influenced by iron overload. Cirrhosis

is defined by METAVIR stage F4[3] Prevalence of liver cirrhosis is reported to be 10-40% and prevalence of liver fibrosis is about 40-80%.[4] By age 3-5years, liver iron concentration may reach values associated with significant risk of liver fibrosis in severe thalassemia. Risk of liver cirrhosis increases at serum ferritin values >1000 ng/ml.[5] Liver fibrosis is an important negative prognostic factor for bone marrow transplantation in beta-thalassemia patients.[6,7] With effective iron chelation, liver fibrosis may be reversible, but liver cirrhosis cannot be reversed.[8] Hence, it is important to detect liver fibrosis early and monitor for progression.

Acoustic radiation force impulse (ARFI) is an ultrasound based elastography to evaluate deep tissue stiffness by virtual touch tissue quantification using conventional probe.[9-11] Speed of propagation of mechanical waves across hepatic parenchyma provides estimate of liver elasticity, which is a surrogate marker of liver fibrosis.

Liver stiffness measurement (LSM) is feasible in children and is related to liver fibrosis.[12]

Mean normal values and mean values indicating severe fibrosis range from 0.8-1.7 m/s and about 1-3.4m/s respectively.[10] ARFI can be used in the study of liver in significant fibrosis or cirrhosis.[10]

METHODS

We conducted a case control study between February 2015 to June 2015 at a tertiary care teaching hospital to measure liver stiffness value in thalassemia patients. Study was approved by institutional ethics committee.

Case

Inclusion criteria: All the thalassemic patients received atleast 10 transfusions attending pediatrics outpatient department or admitted in pediatric ward were included in the study group.

Exclusion criteria: Thalassemic patients with <10 blood transfusion were excluded.

Controls

Inclusion criteria: Nonthalassemic patients with normal liver function tests.

Exclusion criteria: Nonthalassemic patients with abnormal liver function tests.

Assessment of liver stiffness is done by acoustic radiation force impulse elastography performed by the single radiologist using Philips iu22 machine using low frequency C5-2probe. 10 measurements are taken from by right lobe segment 5 of liver about 1 to 2 cm from skin surface and median value is taken. Serum ferritin was measured by particle induced immunoturbidimetric method.

RESULTS

Study sample had 46.9% females and 53.1% males. 56.3% of cases were between 5-10 years, 31.3% were more than 10 years and 12.5% were <5 years. Mean value of liver stiffness in cases was 1.48 m/s, whereas in controls was 1.15 m/s.

Table 1: Liver stiffness values (m/s).

Transient elastography						
	N	Mean ± SD	95% Confidence Interval for mean		t test	p
			Lower bound	Upper bound		
Cases	32	1.4803 ± 0.22324	1.3998	1.5608		0.000
Control	32	1.1500 ± 0.06947	1.1250	1.1750	63.874	<0.001, HS
Total	64	1.3152 ± 0.23368	1.2568	1.3735		

Difference between LSM value between cases and controls were significant with p value <0.001. There were no statistically significant difference in LSM value is seen between cases and controls with respect to age, sex.

DISCUSSION

We investigated to determine the liver stiffness measurements by virtual touch tissue quantification technique in thalassemia patients.

EFSUMB recommends use of point shear wave elastography done by ARFI to assess severity of liver fibrosis in patients with chronic viral hepatitis.[13] It is also been used in study of chronic liver diseases like autoimmune hepatitis, non-alcoholic steatohepatitis, nonalcoholic fatty liver disease, posttransplant patients, Primary biliary cirrhosis, primary sclerosing cholangiohepatitis, hemoglobinopathies. German guidelines have included liver elastography as a potential non-invasive test for excluding liver cirrhosis in chronic viral hepatitis B or C.[14] Information on diagnostic value

of ARFI in assessment of liver fibrosis in non-viral liver disease is limited.

Romanian guidelines recommend to perform 10 valid measurements and calculate their median value as indicator of liver stiffness. It has to be measured 1-2 cm under liver capsule, only in right liver lobe (segment V or VIII). Suggests technical parameters interquartile range <30% and success rate >60% to increase accuracy. Mean LS value in Romanian healthy volunteers is 1.15 m/s (± 0.2) and is not influenced by age and gender.[15]

Hanquinet et al in the study of 103 children found no statistical difference between measurements taken at different ages, and mean propagation velocity is 1.12 m/s.[16] Matos et al. in the study of 150 children found that the mean propagation velocity is 1.07 ± 0.10 m/s, but found a significant difference between age group <6 years and >6 years.[17] Onofrio et al. concludes that the normal mean value of LS is 1.5 m/s in healthy subjects.[10] In our study, mean liver stiffness value is found to be 1.15m/s and were not influenced by age.

Study by Yap et al. shows that ARFI values increases as the fibrosis stages and inflammatory stages increases.[18] Sporea et al. cut off value of 1.21-1.34 m/s for predicting significant fibrosis (F≥2) and 1.8-2 m/s for predicting cirrhosis. (F>4).[19] Goertz et al. in study of chronic liver diseases suggested cut off 1.25 m,/s for F=2, 1.72 m/s for F=3 and 1.75 m/s for F=4 stages and concludes that ARFI elastography value correlates well with degree of hepatic fibrosis.[14] Considering the cut-off values suggested by Goertz et al., in our study, 81.25% of cases were in F=2, 3.12% were in F=3 and 12.5% were in F=4 stage.

Risk of liver cirrhosis increases at serum ferritin values >1000 ng/ml. In our study, liver stiffness value is highly correlated with serum ferritin level (r=0.517, p<0.002).

Most studies included mixed chronic liver disease with predominantly viral hepatitis, cut off value for various etiologies of chronic liver disease needs further evaluation. As per European Association for the Study of the Liver, quality criteria for correct interpretation of pSWE results remains to be defined.[3] Normal cut off value must not be too strict but perhaps they also have to be adapted from time to time, in relation to clinical and technical setting and from measurement to measurement.[10] However, it can be employed in follow-up of cirrhotic patients in order to avoid multiple biopsies comparing result before and after treatment.

To the author's knowledge, this is the first study determined to evaluate the Liver stiffness value in pediatric thalassemic patients.

In our study, Mean value of liver stiffness in cases is 1.48 m/s, whereas in controls it is 1.15 m/s. Difference of liver stiffness value between cases and controls were significant with p value <0.001. Cut off value of 1.24 m/s differentiates between cases and controls with sensitivity 93.8% and specificity 94%. Liver stiffness value is highly correlated with serum ferritin level (r=0.517, p<0.002). There were no statistically significant difference in liver stiffness value between cases and controls with respect to age, sex.

The limitation of the study includes small sample size, convenience sampling, lack of normal values.

We conclude that the ARFI by virtual touch tissue quantification, is useful, non-invasive tool which can be used to detect and follow up liver fibrosis status in thalassemia patients, as it permits evaluation more frequently. Future studies are required to establish the normal value and cut off values of liver stiffness using ARFI virtual tissue quantification technique for determining liver fibrosis.

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Ethical approval: The study was approved by the institutional ethics committee

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