Association of Fibro scan Results with Liver Biopsy and Sonography in Major Thalassemia Patients with Hepatitis C

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ABSTRACT:
Background and Objective: In this study the aim was assessing the changes of liver tissue in major thalassemia patients suffering from hepatitis C with fibro scan test and evaluates the findings’ associations with various parameters of liver function. Patients with β-thalassemia major who regularly receive transfusions are at risk of developing post transfusion hepatitis (PTH). Among these infections, hepatitis B and C are the most common. It is well-known that hepatitis C virus (HCV) is a major cause of PTH infection. A lot of studies among multi-transfused thalassemia patients reported the prevalence of HCV in β-thalassemia patients at a wide range of 3-67.3%. Fibro scan (transient elastography) is a non-invasive sonography-based test which is still not widely used in young thalassemia patients with hepatitis C. Fibro scan measures liver fibrosis and CAP (Controlled Attenuation Parameter) which is equal to percentage of liver fat saturation.

Materials and Methods: This prospective-cohort study was conducted on 150 patients with diagnosis of major thalassemia and hepatitis C in 2015 at Gastroenterology clinic of Baqiatallah hospital. All patients in the study underwent liver biopsy, Doppler sonography of hepatic vessels and fibro scan and evaluated for biochemical markers such as AST, ALT, Ferritin and HCV viral load. Analysis of data was performed by using SPSS (version 21). P value < 0.05 was considered the cut-off value for significance.

Results: All patients were transfusion-dependent and they transfused packed red cells every 28.53 ± 16.48 days. 106 patients had undergone splenectomy while 44 patients hadn’t performed so. HCV viral load was ≤800000 IU/ml in 66% of the patients while in remaining 34% was >800000 IU/ml. There was a significant positive association between results of the fibro scan and liver biopsy. There were also significant positive associations between fibro scan results and AST, ALT, Ferritin and portal vein thickness.

Conclusion: This study indicates that Fibro scan is a precise, accurate and reliable method in liver fibrosis diagnosis but for more definite results, further investigations in a wider study population are mandatory.

Keywords: Hepatitis C, Fibroscan, thalassemia patients, biopsy, biopsy.

[I] INTRODUCTION
Patients with β-thalassemia major who regularly receive transfusions are at risk of developing post transfusion hepatitis (PTH). Among these infections, hepatitis B and C are the most common. It is well-known that hepatitis C virus (HCV) is a major cause of PTH infection, and it can lead to severe inflammation in liver with long-term problems such as disabling symptoms, cirrhosis, and hepatocellular carcinoma. Due to lack of effective vaccine and inadequate infection control policies for HCV poses a significant and growing public health problem in low- and middle-income countries.(1,2)According to the World Health Organization, 170 million of people are infected by HCV in the world. Over 21.3 million of them live in the eastern Mediterranean region. A lot of studies among multi-transfused thalassemia patients reported the prevalence of...
HCV in β-thalassemia patients at a wide range of 3-67.3%. However, under and over reporting trends have also been identified in the intra and inter countries in this region. Mean age, duration, and mean amount of blood transfused have been associated with an increased risk of HCV infection in β-thalassemia patients. Saber-Firoozi et al. stated that the relative risk of HCV infection for each unit of blood transfusion is about 0.2%. Iran is located in the middle of, what is called “the thalassemia belt.” The recent studies in Iran have shown that the prevalence of HCV infection in β-thalassemia patients are different from 2% to 32%.(3-5) On the other hand, iron overload in liver due to frequent blood transfusions is an important precipitating factor for liver fibrosis and cirrhosis in thalassemia patients with concomitant hepatitis C. In adults, non-invasive methods for assessment of liver fibrosis have been accepted widely, in comparison to invasive methods such as liver biopsy. Some guidelines recommend that the first diagnostic step in patients with untreated chronic hepatitis C must be non-invasive tests such as Fibroscan. Another important issue is that beta-thalassemia patients especially those with hepatitis C are more vulnerable to complications of liver biopsy in comparison to other patients suffering from hepatitis C.(6) Fibro scan (transient elastography) is a non-invasive sonography-based test which is still not widely used in young thalassemia patients with hepatitis C. Fibro scan measures liver fibrosis and CAP (Controlled Attenuation Parameter) which is equal to percentage of liver fat saturation. Still liver biopsy is considered as the gold standard diagnostic method in assessing liver fibrosis, despite its invasiveness and complications. Liver biopsy is contraindicated in patients with coagulation impairments and so some physicians tend to perform less-invasive methods such as serologic tests, liver sonography and fibro scintest in initial steps. Liver sonography determines size and shape of liver and further evaluation of liver vessels especially size and thickness of port vein assists diagnosis of liver fibrosis. Liver enzymes’ level and coagulation tests in liver fibrosis patients in combination with sonography and fibro scan aids in more accurate diagnosis of fibrosis and cirrhosis grade. (7-11) In this study the aim was assessing the changes of liver tissue in major thalassemia patients suffering from hepatitis C with fibro scintest and evaluate the findings’ associations with various parameters of liver function.

**[II] MATERIALS AND METHODS**

This prospective-cohort study was conducted on 150 patients with diagnosis of major thalassemia and hepatitis C in 2015 at Gastroenterology clinic of Baqiat-allah hospital. All patients had undertaken frequent blood transfusions and were evaluated for presence of liver fibrosis. All patients were informed of study objectives and were taken informed consent. The inclusion criteria included every major thalassemia patient who was candidate of diagnostic study of liver fibrosis with liver biopsy, Doppler sonography of hepatic vessels and fibro scintest. The exclusion criteria included patients under 12 years old age, presence of concomitant diseases (hemochromatosis, hematologic diseases, other viral infections) and patient’s unwillingness for participation in the study. All patients in the study underwent liver biopsy, Dopplersonography of hepatic vessels and fibroscan. All patients were evaluated for biochemical markers such as AST, ALT, Ferritin and HCV viral load. The demographic data from each patient was collected. Analysis of data was performed by using SPSS (version 21). Student’s t-test for parametric measures and Wilcoxon signed-rank test for non parametric measures was used. Spearman’s rank correlation coefficient was used to correlate between two quantitative variables. P value < 0.05 was considered the cut-off value for significance.

**[III] RESULTS**

**Demographic information**

150 patients with major thalassemia and hepatitis C were enrolled in our study; 90 patients (60%) were male and 60 patients were female (40%).
The total average age was 30.98±6.69 years; this figure was 30.87±7.21 years for males and 31.13±5.89 for females. Patients’ height and weight was 53.02±10.69 kg and 159±11.51 centimeters, respectively. All patients were transfusion-dependent and they transfused packed red cells every 28.53 ± 16.48 days. 106 patients (70.66%) had undergone splenectomy while 44 patients (29.33%) hadn’t performed so.

Biochemical markers
Serum AST level was elevated in 113 patients (75.33%) while in only 37 patients (24.66%) was within normal range. AST level on average was 75.93±62.73 IU/L (range: 15-638). AST level in elevated cases was 91.27 IU/L on average while in normal cases was 20.98 IU/L.

Serum ALT level was elevated in 92 patients (61.33%) while in 58 patients (38.66%) was within normal range. The total AST level was 89.34±91.47 IU/L on average (range: 12-994). ALT level in cases with abnormal level was 122.42 IU/L on average while in normal cases was 36.87 IU/L.

Serum Ferritin level was elevated in 141 patients (94%) and in only 9 patients (6%) was within normal range. The ferritin level was totally 1610.77 mg/ml on average (range: 1430-7455). The ferritin level in patients with elevated ferritin level was 1697.15 mg/ml on average while in normal cases was 158.22 mg/ml on average.

HCV viral load was ≤800000 IU/ml in 66% of the patients while liver fibrosis (TE= 6-12.5 kpa) was seen in 63.33% of the patients. Only 19 patients (12.66%) had normal TE (<6 kpa). There was a significant positive association between results of the fibro scan and liver biopsy (p=0.003). there were also significant positive associations between fibro scan results and AST (p<0.001), ALT (p<0.001), Ferritin (p<0.001) and portal vein thickness (p=0.002).

Fibro scan findings
According to fibro scan findings, liver cirrhosis (TE>12.5 kpa) was detected in 12.66% of the patients while liver fibrosis (TE= 6-12.5 kpa) was seen in 63.33% of the patients. Only 19 patients (12.66%) had normal TE (<6 kpa). There was a significant positive association between results of the fibro scan and liver biopsy (p=0.003). there were also significant positive associations between fibro scan results and AST (p<0.001), ALT (p<0.001), Ferritin (p<0.001) and portal vein thickness (p=0.002).

IV] DISCUSSION
Major thalassemia is an inherited haemoglobiopathy which is common in central Africa, Asia, Pacific Ocean and several parts of India. (12)This disorder is a common condition in Iran, too. (4)Frequent blood transfusions in major thalassemia patients leads to reduction of severe anemia complications and extends life-span of patients but puts the patients at the risk of complications such as Hepatitis C.(13) high prevalence of hepatitis C in thalassemia patients is a serious issue in Iran because screening of blood donors’ for HCV was initiated in 1995 and the first transfusion of a considerable portion of thalassemia patients dates back to before 1995.Many of these patients will suffer from advanced chronic liver disease and their quality of life will be lowered.(9) Liver damage mechanism in infected patients is cellular damage. The intensity of liver damage was associated with vermeil load and severe involvement of liver occurs due to high viral load. Infection with
hepatitis C virus is commonly asymptomatic and follows a chronic course in 50-80% of cases. Chronic persistent/active hepatitis gradually leads to liver fibrosis and eventually ends up in cirrhosis. This course lasts for years and decades after transmission and may lead to hepatocellular carcinoma. (14-18) The factors of hepatitis C disease progression are as follows: duration of infection, age at the time of infection, male gender, alcohol consumption, simultaneous infections of HCV and HBV, concomitant infection with HAV. The role of other factors such as infection source, ethnicity, serum transaminases’ level, peripheral blood platelets’ count, serum albumin level and fibrosis degree has been investigated in previous studies. (19,20) In chronic liver fibrosis, estimation of fibrosis degree and assessment of anti-fibrotic treatments needs precise measures. Liver biopsy has been used as the gold standard method for evaluation of liver inflammation and fibrosis but this method is invasive and even in the expert hands might lead to serious complications such as bleeding, pneumothorax and colon perforation. In addition, serial liver biopsies in short-term reassessment of response to treatment is not feasible and cost-effective. (21-23) The high load of stress and anxiety on the patients while performing liver biopsy must be taken into account. According to the studies, the liver biopsy is 80% accurate, with a risk of both underestimating and over staging and cirrhosis can be missed in ~20% of patients. Even if an expert physician performs liver biopsy and an experienced pathologist interprets tissue specimen, more than 20% error in fibrosis staging is reported. So the need for a non-invasive method for fibrosis diagnosis is undeniable. (24-30) We in this study found significant associations between the results of fibro scan and biopsy findings, AST, ALT, Ferritin levels and portal vein thickness. Elalfy et al reported a positive strong association between liver fibrosis degree and fibro scan results in major thalassemia patients with hepatitis C and concluded that liver fibro scan test is a reliable method for assessment of liver fibrosis in this subgroups of patients. Uyar et al declared that although safer methods as alternative diagnostic modalities for liver biopsy is needed but still liver biopsy maintains its place as the gold standard for diagnosis of histopathological changes in liver tissue. Hermeziu et al reported that fibro scan is an acceptable method in diagnosing liver fibrosis. Other studies have altogether reached a consensus that fibro scan is an available, non-invasive and appropriate method which is validated in Caucasian and Asian patients with chronic hepatitis B and C. (30-35)

[V] CONCLUSION
This study indicates that Fibro scan is a precise, accurate and reliable method in liver fibrosis diagnosis but for more definite results, further investigations in a wider study population are mandatory.

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