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Evaluation of Portal Hypertension Doppler Parameters after Hepatitis C Virus Eradication in Patients with Definite Fibrosis

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Abstract

Backgrounds and aims: Eradication of hepatitis C virus (HCV) infection with direct-acting antivirals (DAAs) nowadays is almost always successful and sustained virological response (SVR) occurs in more than 90% of cases and this prevent more fibrosis and preclude the progression of portal hypertension (PH). We aimed to evaluate the portal hypertensive Doppler parameters as a marker of PH after treatment of HCV with DAAs.

Methods: 200 patients with post chronic HCV infection and definite liver fibrosis ≥F2 were included. All patients underwent laboratory investigations (liver function tests, complete blood count and serum creatinine), abdominal ultrasonography (US), portal Doppler US, fibroscan and upper endoscopy examinations. All patients were treated with DAAs for 12 weeks and then reevaluated for laboratory tests, fibroscan and hepatic Doppler US at the end of treatment and 6 months later. Comparison between those investigations at baseline, end of treatment and 6 months after treatment was analyzed.

Results: 120 females (60%) and 80 males (40%) were included. Their mean ages were 45.0±12.9; and mean Child-Pugh score was 6.35±1.2. The mean baseline value for fibroscan was 16.17±3.9 kPa; thirteen of them (6.5%) were F2, 63 (31.5%) were F3 and 124 (62%) were F4. Liver function tests including serum bilirubin and albumin, prothrombin time and concentration (PT& PC), liver enzymes (ALT and AST) were improved with variable significant values 6 months after treatment. Also Hemoglobin and platelet count were significantly increased both at the end of treatment and 6 months later. Fibroscan values decreased significantly both at the end of treatment and 6 months later (P value= 0.001 and 0.000 respectively). Portal hypertensive parameters including portal vein velocity (PVV), portal volume flow (PVF), portal hypertensive index (PHI), congestion index of portal vein (CI) and Spleno-portal index (SPI) were improved significantly both at the end of treatment and 6 months later (P value= 0.001 and 0.000 respectively, for all parameters). Patients without esophageal varices (OVs) showed more significant degrees of improvement in both fibroscan and portal hypertensive parameters than those with varices.

Conclusions: Doppler portal hypertensive parameters, as a marker of portal hypertension, were improved in parallel with the improvement in fibroscan values after viral clearance and its improvement in early conditions in the current study mandate urgent treatment to avoid possible complications.

Keywords: Portal Hypertension, Doppler US, HCV

Introduction

HCV is considered a major cause of chronic hepatic disease worldwide with a significant variable prevalence, related to the investigated geographic location (1). Millions of people worldwide are chronically infected with HCV. **(2)** Decompensated liver cirrhosis post chronic HCV infection occurs in about 30% of patients within10 years. **(3)**

PH is the increase in portal venous pressure above normal (10 mmHg). **(4).** It is a common complication of liver cirrhosis which leads to the formation of varices (gastro-esophageal), ascites, porto-pulmonary hypertension, hepato-pulmonary syndrome, hepatorenal syndrome, and hepatic encephalopathy. **(5)**

PH occurs due to increase in portal blood flow and intrahepatic vascular resistance; which, has fixed and functional components. The fixed one is secondary to sinusoidal fibrosis, compression by regenerating nodules and relative obstruction in the terminal venules of the portal vein and the functional component is related to the decrease in intrahepatic nitric oxide and the increase in vasoconstrictor substances. **(6)**

Treatment and eradication of HCV infection, with DAAs, till achievement of SVR can improve fibrosis and so, reduce the disease-related morbidity and mortality**. (7)** And this was proved by significant regression of the parameters of transient elastography after SVR.**(8)**

Fibroscan is used to determine the degree of liver fibrosis but, its role in assessment of PH and prediction of varices is controversial.(9) Also, Color Doppler ultrasound can be used noninvasively to assess the degree of inflammation and fibrosis in patients with chronic viral hepatitis. **(10)**

Multiple parameters, which could be measured with Doppler ultrasound, are reported to be altered with the progression of hepatic fibrosis and are considered as markers of PH, such as, PVV, PVF, PHI, SPI, and CI. (**11-12**).

The aim of the study

To assess the dynamic changes in portal hypertensive Doppler parameters in patients with chronic HCV infection (as a marker of portal pressure) and the degree of hepatic fibrosis before and after treatment with DAA therapy.

Materials and Methods

This prospective observation study was conducted on two hundred patients with post chronic HCV infection with definite liver fibrosis (≥F2), from November 2016 to September 2017, attending the Out-patient clinics of Tropical Medicine & Gastroenterology and Internal Medicine Department, Qena University Hospital.

The diagnosis of post chronic HCV infection liver cirrhosis was confirmed by clinical examination, laboratory parameters (liver functions test, CBC, INR, the presence of antibodies against HCV and positive PCR HCV RNA by real-time PCR). Included patients underwent: (1) fibroscan (using FS-502 touch device, France): patients with fibrosis score < f2 were excluded.(2) Abdominal ultrasound imaging which was done 8 hours after the last meal, The liver was assessed for size, surface, parenchymal echogenicity, borders, the diameter of the portal veins. Spleen size and the degree of ascites were recorded. (3) Duplex Doppler ultrasound was performed for all patients at radio-diagnosis department using logic P6 GE ultrasound system with convex probe 3.5MHZ for identification of portal vein, hepatic artery, splenic vein& splenic artery. Pulsed Doppler was performed for three settings before, at& 6month after completion of treatment. The patient was fasting overnight and was positioned in the supine position with breath-holding after shallow inspiration with an angle less than 60 degree between the vessel & US beam. The Doppler sample volume cursor was positioned in the center of the vessel lumen. The following parameters were measured: portal vein diameter, cross-sectional area& velocity (PVV) (minimum, maximum & average) portal vein flow, resistivity & pulsatility indices of hepatic and splenic arteries. Indices for portal hypertension were calculated as follow: (1) Portal vein flow volume

(PVF) (ml/min) = Vmean x CSA x 60 (13). (2) Portal vein Congestion index (CI) (cm/s-1) = CSA / mean velocity (14). (3) Portal hypertension index (PHI) (cm/s-1) = [(hepatic artery RI x 0.69) x (splenic artery RI x 0.87)]/portal vein mean velocity (15). (4) Splenoportal index (SPI) = splenic index (SI) / portal vein velocity, where SI= SI = A x B, where A is the transverse splenic diameter in centimeters and B is the vertical diameter in centimeters at the maximal cross-sectional images of the spleen **(16).** (4) Upper endoscopy examination was done for all patients (using Olympus, GIF-XQ260 instrument) to detect the presence or absence of esophageal or gastric varices. Esophageal varices were graded into grade I: enlarged but straight varices, grade II: enlarged tortuous varices and grade III: coiled shaped markedly enlarged varices **(17).**

All patients were treated according to the Egyptian protocol for treatment of chronic HCV infection by Sofosbuvir (400 mg) and Daclatasvir (60 mg) ± ribavirin (800-1200 mg) daily for 12 weeks.

Patients were reevaluated at the end of treatment and 6 months after complete the treatment by liver functions test, abdominal ultrasound, fibroscan and color Doppler ultrasound.

Patients with co-infections with HIV or HBV, malignant liver or malignancy anywhere in the body, autoimmune disease, other causes of liver disease, using immunosuppressive drugs, use of any medications that could alter the measurements of Doppler parameters, history of band ligation or sclerotherapy for varices, history of acute bleeding varices and pregnant women were excluded.

Statistical analysis:

Data entered and analyzed using statistical package of social science (SPSS) version 16. The data are presented as means ± SD or number (%). Paired Student's-*t*-test was used to assess the significance in laboratory, Doppler and fibroscan parameters pre-treatment and at the end of treatment and also, pre and after 6 months of therapy. Assessment of correlations and relations was analyzed using Sperman correlation coefficient. The significance was established at $p < 0.05$.

Ethical approval:

The protocol of the study was locally approved by the ethical committee in our institution and all included patients provided informed consent before conducting the study.

Results

The current study included 200 patients with HCV infection with their mean ages were 45.0±12.9; 120 females (60%) and 80 males (40%) and their mean Child-Pugh score was 6.35±1.2. All patients showed SVR after 24 weeks of completion of treatment (100%). Esophageal varices were found in 64 patients (32%) and the commonest grade was grade I; in 46 patients (23%). The mean value for fibroscan was 16.17±3.91 kPa; thirteen of them (6.5%) were F2, 63 (31.5%) were F3 and 124 (62%) were F4. This is illustrated in table 1.

Table 1. Demographic data for patients at base line

Parameter	Value
Number (=n)	200
Age	45.0±12.9
Gender	
Male	120 (60%)
female	80 (40%)
Child-Pugh score	6.35±1.2
Varices(Esophageal)	
(yes/no)	(64/136)
Grades of varices	
(I/II/III)	(46/14/4)
Fibroscan(kPa)	16.17±3.91

All data are expressed as number, %.

- Laboratory parameters: there was statistically significant improvement in the liver function tests 6 months after therapy with DAAs; including serum bilirubin, albumin, total protein, prothrombin time and concentration, and liver enzymes. Only prothrombin time and concentration showed statistically significant improvement at the end of treatment. Also, hemoglobin and platelet count were significantly increased both at the end of treatment and 6 months later, table 2.

Table 2. Mean serum laboratory data for all patients at base line, end of treatment and 6 months after treatment

Parameter	Base line	End of treatment	P value	After 6 months	P value
Bilirubin (mg/dl)	1.5±0.43	1.4±0.31	NS	1.1±0.09	0.000
Protein (g/dl)	7.63±1.8	7.71±1.6	NS	7.86±1.9	0.02
Albumin (g/dl)	3.71±0.42	3.78±0.34	NS	3.81±0.59	0.001
ALT (U/L)	42±34.04	38±21.3	NS	30±12.6	0.000
AST (U/L)	40.4±13.2	36.8±14.5	NS	28.3±13.8	0.000
Prothrombin time (sec)	11.6±2.21	11.2±2.09	0.004	11.0±1.02	0.000
Prothrombin conc. (%)	70.3±10.8	72.6±9.9	0.004	75.1±10.2	0.000
Hemoglobin (g/dl)	12.21±1.36	12.6±1.61	0.04	13.0±1.24	0.001
WBC (10^3/µl)	6.92±2.41	6.86±2.73	NS	6.81±2.82	NS
Platelet Count (10^3/µl)	209.5±51.53	218.3±63.2	0.03	234.6±49.79	0.000
Serum creatinine (mg/dl)	0.86±0.21	0.87±0.19	NS	0.87±0.20	NS

All data are expressed as mean±SD, student -t- test was used, NS= non significant

- Doppler parameters: there was significant improvement in Doppler parameters at the end of treatment (P value = 0.000 for all parameters) and more degree of improvement after 6 months of treatment (P value = 0.000 for all parameters). Significant increases were noted in PVV, PVF and a significant reduction in CI of the portal vein, PHI, and SPI (P value = 0.000 for all parameters), table 3.

- Fibroscan measures were significantly reduced at the end of treatment with more reduction after 6 months of treatment (P value = 0.000), table 3.

Table 3. Doppler parameters and fibroscan at base line, end of treatment and 6 months after treatment

Parameter	Base line	End of treatment	*P* value	After 6 months	*P* value
PVV(cm/s)	13.61±2.53	14.72±2.67	0.001	15.81±2.067	0.000
PVF(ml/min)	927.1±108	940.7±106	0.001	960.4±120.7	0.000
CI(cm/s^{-1})	0.0705±0.0739	0.059±0.062	0.001	0.054±0.052	0.000
PHI(cm/s^{-1})	1.62±0.254	1.49±0.36	0.001	1.47±0.27	0.000
SPI	5.89±0.28	4.51±0.312	0.001	3.88±0.19	0.000
Fibroscan(kPa)	16.17±3.91	15.01±3.24	0.001	14.16±4.1	0.000

All data are expressed as mean±SD. Student t test was used, *P* value significant < 0.05.

- When we classified patients according to the presence of varices into patients with and without varices: patients without varices showed more improvement in both fibroscan and parameters of portal hypertension than in patients with varices at the end of treatment and 6 months later, this is illustrated in table 4.

Table 4. Doppler parameters and fibroscan at base line, end of treatment, 6 months after treatment in patients with and without varices

Parameter	Base line	End of treatment	*P* value	After 6 months	*P* value
PVV(cm/s)					
With	12.94±2.4	13.87±2.5	0.03	15.3±2.4	0.001
without	14.88±2.6	15.54±2.9	0.001	17.1±2.3	0.000
PVF(ml/min)					
With	912.2±98	920.3±112	0.04	945±104	0.001
without	980.1±101	1050.2±118	0.001	1120±134	0.000
CI(cm/s-1)					
With	0.079±0.08	0.071±0.02	0.03	0.069±0.08	0.001
without	0.0613 ± 0.1	0.050±0.06	0.01	0.049±0.05	0.000
PHI(cm/s-1)					
With	1.72±0.3	1.68±0.4	0.01	1.59±0.1	0.001
without	1.57± 0.6	1.51±0.2	0.01	1.41±0.7	0.001
SPI					
With	6.90±0.2	6.11±0.3	0.001	5.10±0.3	0.000
without	3.59±0.5	3.01±0.4	0.001	2.8±0.1	0.000
Fibroscan(kPa)					
With	16.9±4.1	16.6±3.8	0.04	15.5±3.9	0.001
without	15.1±3.7	14.6±3.1	0.02	13.7±3.1	0.000

All data are expressed as mean±SD. Student-t- test was used, *P* value significant < 0.05.

Table 5. Correlations between Doppler parameters and fibroscan at base line

Variable	rho	P value
PVV	-0.437	0.000
PVF	-0.421	0.000
CI	+0.136	0.05
PHI	+0.942	0.000
SPI	+0.832	0.000

Sperman correlation test was used.

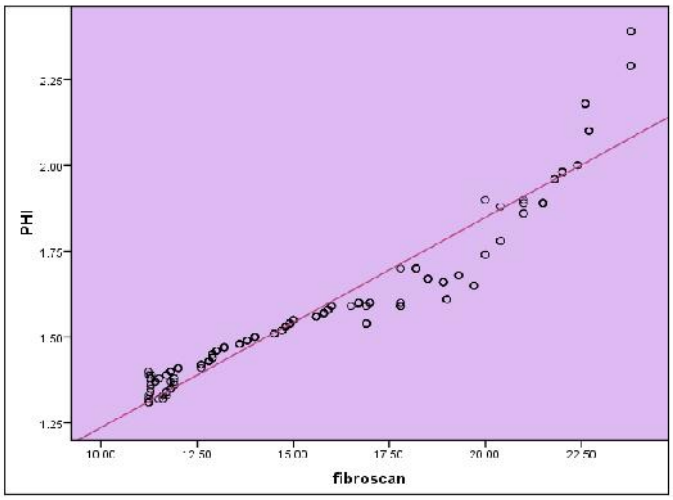

Figure 1. Correlation between fibroscan and PHI at base line (rho=+0.942, P value=0.000)

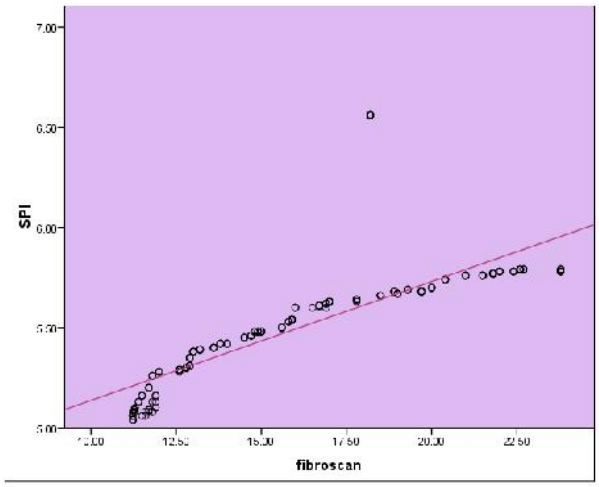

Figure 2. Correlation between fibroscan and SPI at base line (rho= +0.832, P value=0.000)

Discussion

Eradication of HCV infection is an urgent medical seek so as to prevent more progression of liver fibrosis with subsequent cirrhosis and its complications including liver cell failure and portal hypertension. This study aimed to evaluate the degree of changes in Doppler portal hypertensive parameters by Doppler ultrasonography after successful eradication of HCV infection in patients with definite fibrosis and also the degree of changes in hepatic fibrosis by fibroscan.

In this study, all patients achieved SVR with significant improvement in liver function tests 6 months after viral eradication. This comes in agreement with the study conducted by **Deterding et al., 2015** who conducted their study on patients with advanced liver cirrhosis and concluded that treatment with interferon-free regimens cause improvement in liver function, and decrease the need for hepatic transplantations **(18).**

Also in this study we found significant regression in fibroscan value detected in all patients at the end of treatment and 6 months post-treatment, also the study done by Jacqueline et al., 2017 showed that patients with SVR after DAA therapy showed marked improvement in median transient elastography values from 12.65 kPa to 8.55kPa (**8**).

In this study, Doppler indices of PH (PVV, PVFV, PHI, CI, and SPI) were improved, at the end of treatment and 6 months later, to a certain significant degrees that suggest a reduction in portal pressure, which is considered to be beneficial for patients to prevent more elevation of portal pressure.

Hepatic venous pressure gradient (HVPG) which detects the degree of PH invasively was measured in two studies using interferon-based therapy. The first one showed modest reduction 6 months after treatment **(19).** The second one used triple therapy and showed a significant reduction in both HVPG and liver stiffness 6 months after treatment (10.3 mmHg vs 6.1 mmHg and 21.3 kPa vs 6.4 kPa, $P < 0.001$) **(20).** In another study, using DAAs, 33 cirrhotic patients included and treated with 48 wk sofosbuvir + ribavirin with clinically significant PH at baseline, 24% achieved a ≥ 20% decrease in HVPG at the end of treatment, although the median HVPG change in the entire cohort was modest (-0.5 mmHg) **(21).**

Up to date, this study is one of the recent researches that evaluated the changes in Doppler ultrasound parameters after eradication of HCV with DAAs. Reduction of PH after curative treatment of HCV infection is due to stoppage of liver inflammation, liver fibrosis and mechanical structural changes that share in the pathophysiology of PH.

In the current study, we noted good correlations between Doppler ultrasound parameters and fibroscan measures before starting treatment indicating that more fibrosis is associated with more structural changes related to subsequent development of PH, and reduction of fibrosis is reflected in lowering portal pressure.

In this study, the degree of improvements in both fibroscan and PH Doppler parameters measures were more significant in patients with no varices than those with varices so, early detection and early management will lead to significant structural improvement which could avoid and stop the formation and development of varices.

Deterding et al suggested a two-phasic reduction in PH consisting of a rapid first phase during treatment (related to improved inflammation) then a second slower phase after 6-12 months (related to fibrosis regression). **(22)**

Conclusions

Doppler portal hypertensive parameters, as a marker of portal hypertension, were improved in parallel with improvement in fibroscan values after hepatitis C viral clearance and its improvement in early conditions mandate urgent treatment to avoid possible hazardous complications.

Conflict of interest

All Authors declared that no conflict of interest and no financial support from any agency.

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