Evaluation of the Effect of Propranolol on Portal Hemodynamics in Patients with HCV-Related Cirrhosis

Ahmad Abdel Bary Abdel Rahman[1]; Riham Mohamed Elshafie [2]; Heba Mohamed Abdella[3]; and Mohamed Shaker Ghazy [4]

[1]Pharmaceutics and Industrial Pharmacy Department, Ex-Dean, Faculty of Pharmacy, Cairo, Ex-Dean, Faculty of Pharmacy, Beni Suef, Cairo University
[2]Clinical Pharmacy Department,Ain Shams Specialized Hospital. Cairo, Egypt.
[3]Tropical Medicine Department; Faculty of Medicine, Ain Shams University, Cairo, Egypt
[4]Radiodiagnosis Department; Faculty of Medicine, Ain Shams University, Cairo, Egypt

Abstract: Background─ Propranolol is commonly used in the prophylaxis of variceal haemorrhage in cirrhosis which is a life-threatening complication by reducing portal pressure and variceal pressure.
Aim of the work─ Evaluation of the effect of varying doses of Propranolol on portal hemodynamics in patients with HCV-related cirrhosis measured by specific parameters in Doppler ultrasonography.
Patients and methods─ 60 cirrhotic patients due to HCV with portal hypertension proved by oesophageal varices (o.v) in upper endoscopy; were divided into three groups and given oral propranolol in doses of 30mg/day, 60mg/day and 90mg/day respectively for one week. All patients were subjected to full history taking, thorough clinical examination, laboratory investigations, abdominal ultrasonography using duplex Doppler ultrasonography before and one week after drug administration was done for detecting changes of medication on portal hemodynamics which include portal vein diameter, mean velocity (Vmean), maximum velocity (Vmax), portal flow volume (PFV), cross sectional area (CSA) and congestion index (CI).
Results─ Propranolol in all three doses (30mg, 60mg and 90mg) reduced the heart rate. Regarding portal hemodynamics propranolol in doses of 30mg and 60mg showed no significant change in all mentioned portal hemodynamics. However, propranolol in a dose of 90mg showed significant change in Vmean, Vmax and PFV.
Conclusions─ Commonly used doses of propranolol (30-60mg/day), showed no significant difference on portal hemodynamics. While propranolol in a dose of 90mg/day showed a significant positive change on Vmean, Vmax and PFV. Patients receiving propranolol must be cautiously monitored regarding the reduction in heart rate.
[Ahmad Abdel Bary Abdel Rahman; Riham Mohamed Elshafie ; Heba Mohamed Abdella and Mohamed Shaker Ghazy. **Evaluation of the Effect of Propranolol on Portal Hemodynamics in Patients with HCV-Related Cirrhosis.** Journal of American Science 2012; 8(3): 447-456]. (ISSN: 1545-1003). http://www.americanscience.org. 60

Keywords: portal hypertension, propranolol, Doppler ultrasonography, portal vein diameter, congestion index, portal hemodynamics.

Abbreviations: **HCV:** Hepatitis C Virus **PFV:** Portal Flow Volume **CSA:** Cross Sectional Area **CI:** Congestion Index **Vmean:** mean portal flow velocity **Vmax:** maximum portal flow velocity

1. Introduction

Propranolol and other β-blocking agents have been used for prophylaxis of gastrointestinal bleeding in adults with portal hypertension since the first published report by **Lebrec et al. (1981)**. Most experience has been gained with this usage in patients with chronic liver disease or cirrhosis **(Samy, 2010).**

Portal hypertension is one of the most life threatening complications of cirrhosis leading to ascites and esophageal varices. Consequences of portal hypertension are caused by blood being forced down alternate channels by the increased resistance to flow through the systemic venous system rather than the portal system (**Garcia-Tsao G., 2011).**

Normal portal pressure is generally defined between 5 and 10 mm Hg. However, once the portal pressure defined as a portal pressure gradient (the difference in pressure between the portal vein and the hepatic veins) rises to 12 mm Hg or greater, complications can arise, such as varices and ascites (**Toubia and Sanyal 2008).**

Variceal bleeding constitutes the most significant life-threatening clinical sequela of portal hypertension. The prevalence of varices in such patients is variable and is reported to be between 24% and 69% **(Albillos, et al., 2010)**.

Mortality associated with first episode of variceal bleeding ranges from 5% to 10% in cirrhotic patients, the range is from 40% to 70% **(Clifford, 2004).**

Doppler ultrasonography remains the first step in the evaluation of patients with liver cirrhosis and portal hypertension. It is easy and fast to perform and supports imaging with significant clinical information regarding flow direction and quantification **(Goyal, et al., 2009 and Simonetti, 1999)**. It has an important role to understand the vascular hemodynamics in patients with cirrhosis and recognition of the degree of liver dysfunction **(Abdel-Mageed M., (2000).**

Portal hemodynamics involved are: portal vein diameter and flow velocity that can be visualized by Doppler ultrasonography **(Eugene, et al., 2011).**

Thereby; cross sectional area, portal flow volume and congestion index can be calculated.

This study was conducted to identify the effect of propranolol as a non selective beta-blocker on portal hypertension using the changes in portal hemodynamics detected by using duplex Doppler technique.

2. Patients and Methods

60 cirrhotic patients with portal hypertension (HCV+ve) were randomly selected and classified into three groups (20 patients each). All patients (32 males and 28 females) subjected to full history taking and thorough clinical examination for the manifestations of: liver cell failure, cardiac examination and chest examination. Heart rate, laboratory investigations included liver profile, complete blood picture, kidney function tests, hepatitis markers, chest x-ray and ECG. Upper GI endoscopy was done for detection of oesophageal varices. Abdominal ultrasonography was performed by one examiner (to avoid inter-observer variability) who was unaware of the patient clinical or laboratory data.

Color Doppler ultrasonographic study of portal haemodynamics was done with stress on portal vein diameter (PVD), mean portal vein velocity (Vmean), Portal vein cross sectional area (CSA), congestion index (CI), where CI = A (area) / Vmean

Portal vein flow volume (PFV), where PVF=CSA X Vmean X 60

Each group received its determined dose during the study as follows: group I: 10mg oral propranolol three times daily, group II: 20mg three times daily and group III: 30mg three times daily for one week. Particular attention was given to adherence, side effects, and the necessity for discontinuing the medication.

The effect of propranolol on portal hemodynamics were assessed before and one week after, using Doppler ultrasonography.

3. Results

The study included 32 males and 28 females with age 51.8±6.8633 with proven chronic liver disease (HCV+ve) at varying stages and portal hypertension. The diagnosis of chronic liver disease was based on clinical, laboratory and ultrasonographic findings. Exclusion criteria included hepatocellular carcinoma, splenic or portal vein thrombosis, diabetes mellitus, bronchial asthma, heart block and pregnancy.

Patients were classified into three groups according to non selective beta-blocker (propranolol) therapy.

Group I: included 20 patients who received 10 mg propranolol tablet three times daily. Group II: included 20 patients who received 20 mg propranolol tablet three times daily. Group III: included 20 patients who received 30 mg propranolol tablet three times daily. All patients were prospectively followed up from the time of admission until the end of the study (one week after).

All patients underwent upper GI endoscopy which proved the presence of oesophageal varices due to portal hypertension.

As regard heart rate before and after treatment in group I it showed a mean value of 82.2 before treatment and 79.4 after treatment with a highly significant change and a negative delta change mean value -0.034 Table (1).

The comparison in group I pre and post treatment as regard Doppler findings is demonstrated, in table (2), as follows:

a) Portal vein diameter

There was no significant difference (P-value > 0.05) with a mean value of 14.66 before treatment and 14.56 after treatment in group I.

b) Mean value of portal vein velocity

There was no significant difference (P-value > 0.05) with a mean value of 8.7 before treatment and 8.64 after treatment in group I.

c) Mean value of portal vein cross sectional area of

There was no significant difference (P-value > 0.05) with a mean value of 1.697 before treatment and 1.671 after treatment in group I.

d) Mean value of portal vein flow volume

There was no significant difference (P-value > 0.05) with a mean value of 868.9 before treatment and 850.45 after treatment in group I.

e) Mean value of portal vein congestion index

There was no significant difference (P-value > 0.05) with a mean value of 0.2022 before treatment and 0.2002 after treatment in group I.

As regard heart rate before and after treatment in group II it showed a mean value of 79.55 before treatment and 72.2 after treatment with a highly significant change and a negative delta change mean value -0.0921 Table (3).

The comparison in group II before and after treatment as regard Doppler parameters is demonstrated in table (4) as follows:

a) Portal vein diameter

There was no significant difference (P-value > 0.05) with a mean value of 14.8 before treatment and 14.72 after treatment.

b) Mean value of portal vein velocity

There was no significant difference (P-value > 0.05) with a mean value of 8.704 before treatment and 8.65 after treatment.

c) Mean value of portal vein cross sectional area of

There was no significant difference (P-value > 0.05) with a mean value of 1.72 before treatment and 1.706 after treatment.

d) Mean value of portal vein flow volume

There was a no significant difference (P-value > 0.05) with a mean value of 894.75 before treatment and 883 after treatment.

e) Mean value of portal vein congestion index

There was no significant difference (P-value > 0.05) with a mean value of 0.202 before treatment and 0.2 after treatment.

As regard heart rate before and after treatment in group III it showed a mean value of 76.8 before treatment and 60.05 after treatment with a highly significant change and a negative delta change mean value -0.2166 Table (5).

The comparison in group III before and after treatment as regard Doppler parameters is demonstrated in table (6) as follows:

a) Portal vein diameter

There was a non-significant decrease (P-value > 0.05) with a mean value of 14.67 before treatment and 14.58 after treatment.

b) Mean value of portal vein velocity

There was a significant decrease (P-value < 0.05) with a mean value of 11.37 before treatment and 11.10 after treatment.

c) Mean value of portal vein cross sectional area of

There was a non-significant decrease (P-value > 0.05) with a mean value of 1.694 before treatment and 1.657 after treatment.

d) Mean value of portal vein flow volume

There was a significant decrease (P-value < 0.05) with a mean value of 1168.4 before treatment and 1092.8 after treatment.

e) Mean value of portal vein congestion index

There was a non-significant decrease (P-value > 0.05) with a mean value of 0.1514 before treatment and 0.148 after treatment.

A Multiple comparison between the three studied groups as regard heart rate using delta change for finding the actual difference in heart rate pre and post treatment showed no significant difference between groups I and II, I and III, II and III before treatment. And it showed a significant decrease in heart rate between groups I, II. High significant decrease between groups II, III and I, III (table 7).

A multiple comparison between each two groups of the three studied groups using delta change for finding the actual change in portal hemodynamics using Doppler technique pre and post treatment showed no significant change between the groups I and II, I and III, II and III before treatment. The results were as follows (table 8):

a) Portal vein diameter

There was no significant difference (P-value > 0.05) between each two groups.

b) Mean value of portal vein velocity

There was no significant difference (P-value > 0.05) between groups I, II. But, there was a significant difference between groups I, III and II, III (P-value < 0.05).

c) Mean value of portal vein cross sectional area

There was no significant difference (P-value > 0.05) between each two groups.

d) Mean value of portal vein flow volume

There was no significant difference (P-value > 0.05) between groups I, II. But, there was a significant difference between groups I, III and II, III (P-value < 0.05).

e) Mean value of portal vein congestion index

There was no significant difference (P-value > 0.05) between each two groups.

As regard Child Pugh's classification of cases in the three groups; there was no change detected before and after treatment.

Table (1): Comparison in group I as regard cardiovascular examination (heart rate) before and after treatment

	Group I					
	Before		After		Sig.	Delta change mean value
	Mean	S.D.	Mean	S.D.		
Heart rate	82.2	7.19	79.4	6.86	HS	-0.034

Table (2) Comparison in **group I** as regard **Doppler parameters** before and after treatment

	Group I					
	Before		After		P value	Sig.
	Mean	S.D.	Mean	S.D.		
Vmax.	14.96	2.078	14.88	2.031	0.303	NS
Vmean	8.7	1.318	8.64	1.291	0.178	NS
PVD	14.665	1.075	14.56	0.954	0.071	NS
CSA	1.697	0.242	1.671	0.213	0.056	NS
PFV	868.9	168.60	850.45	158.13	0.068	NS
CI	0.2022	0.0376	0.2002	0.0349	0.326	NS

Table (3) Comparison in group II as regard cardiovascular examination (heart rate) before and after treatment

Group II						
	Before		After		Sig.	Delta change mean value
	Mean	S.D.	Mean	S.D.		
Heart rate	79.55	3.8	72.2	3.39	HS	-0.0921

Table (4) Comparison in group II as regard Doppler parameters before and after treatment.

Group II						
	Before		After		P value	Sig.
	Mean	S.D.	Mean	S.D.		
Vmax.	15.26	1.959	15.18	1.871	0.297	NS
Vmean	8.704	1.125	8.65	1.067	0.247	NS
PVD	14.8	0.730	14.72	0.638	0.19	NS
CSA	1.72	0.170	1.706	0.149	0.175	NS
PFV	894.75	103.04	883	98.89	0.115	NS
CI	0.202	0.038	0.2	0.034	0.314	NS

Table (5) Comparison in group III as regard cardiovascular examination (heart rate) before and after treatment

Group III						
	Before		After		Sig.	Delta change Mean value
	Mean	S.D.	Mean	S.D.		
Heart rate	76.8	4.08	60.05	3.47	HS	-0.2166

Table (6) Comparison in group III as regard Doppler findings before and after treatment.

Group III						
	Before		After		P value	Sig.
	Mean	S.D.	Mean	S.D.		
Vmax.	19.96	3.278	19.47	3.16	0	S
Vmean	11.37	1.85	11.10	1.81	0	S
PVD	14.67	0.735	14.58	0.674	0.17	NS
CSA	1.694	0.171	1.657	0.153	0.19	NS
PFV	1168.4	280.72	1092.8	249.9	0	S
CI	0.1514	0.022	0.148	0.02	0.312	NS

Table (7) multiple comparison between the three studied groups as regard heart rate before and after treatment.

	Groups		P	Sig.
HR-B	1	2	0.116	NS
	1	3	0.102	NS
	2	3	0.104	NS
HR-A	1	2	0.042	S
	1	3	0.008	HS
	2	3	0.019	HS
HR-dc	1	2	0.039	S
	1	3	0.007	HS
	2	3	0.021	HS

Table (8) Multiple comparison between the three groups as regard Doppler parameters using delta change:

Parameter	Groups		P	Sig.
Vmax-dc	1	2	0.952	NS
	1	3	0.004	S
	2	3	0.003	S
Vmean-dc	1	2	0.853	NS
	1	3	0.009	S
	2	3	0.005	S
PVD-dc	1	2	0.695	NS
	1	3	0.703	NS
	2	3	0.921	NS
CSA-dc	1	2	0.696	NS
	1	3	0.831	NS
	2	3	0.751	NS
PFV-dc	1	2	0.58	NS
	1	3	0.28	S
	2	3	0.41	S
CI-dc	1	2	0.916	NS
	1	3	0.537	NS

	2	3	0.47	NS

Table (9) Complaints and side effects detected in the three groups during therapy.

Complaints / Groups	Fatigue	Mild broncho-constriction	No complaints
Group I	3(15%)	2(10%)	15(75%)
Group II	4(20%)	2(10%)	14(70%)
Group III	8(40%)	3(15%)	9(45%)

Complaints and side effects detected increased by increasing the dose of propranolol.

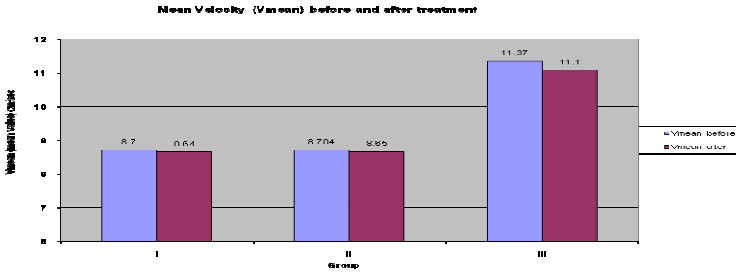

Fig. (1): comparison between Vmean in all groups before and after treatment

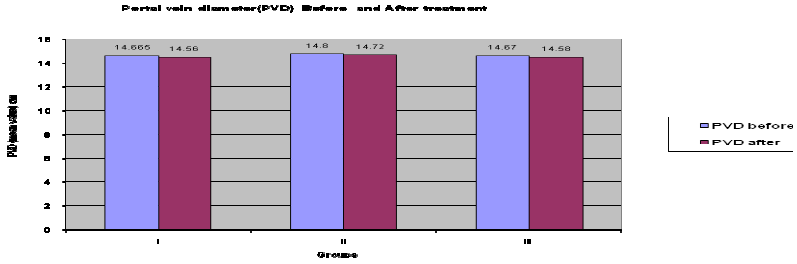

Fig. (2): comparison between PVD in all groups before and after treatment

4. Discussion

Liver cirrhosis due to chronic liver disease is one of the major health problems causing portal hypertension. Consequences of portal hypertension are caused by blood being forced down alternate channels by the increased resistance to flow through the systemic venous system rather than the portal system.

Portal hypertension and its consequence gastro-oesophageal bleeding from varices is the most life threatening complication in the liver cirrhosis **(Garcia and Laurie, 2011).**

Bleeding oesophageal varices is the gravest complication of liver cirrhosis, with a high mortality and each variceal bleeding attack carries a mortality rate of 17%-57%, these data reflects the importance to find a reliable noninvasive method for detection of oesophageal varices specially when the number of patient requiring endoscopic screening is in millions, which is the situation in Egypt **(Serag and Omran, 2011),** and it is considered to be the main cause of upper gastrointestinal bleeding. Each episode of bleeding has a 30%–50% mortality risk. Furthermore, after the initial episode of bleeding the incidence of rebleeding is up to 70% and frequently occurs within 6 weeks of the initial hemorrhage **(Toubia and Sanyal 2008).**

Doppler ultrasonography remains the first step in the evaluation of patients with liver cirrhosis and portal hypertension. It is easy and fast to perform and supports imaging with significant clinical information regarding flow direction and quantification (**Goyal, et al., 2009 and Simonetti, 1999**). It has an important role to understand the vascular hemodynamics in patients with cirrhosis and recognition of the degree of liver dysfunction **(Abdel-Mageed, et al., 2000).**

In fact, treatment with nonselective ß-blocker therapy shows evidence of reducing the risk of primary bleeding of esophageal varices by up to 50%. Along with decreasing the risk of bleeding comes a reduction in mortality by 25%–45% when compared to no therapeutic intervention **(Thuluvath, et al., 2005).**

Meta-analyses also support these results by showing a 40% decrease in bleeding risk in patients with whom nonselective ß-blocker therapy is used **(Wilbur, et al., 2005).**

Regarding varices, it is well established that if the hepatic venous pressure gradient (HVPG) can be reduced to less than 12 mm Hg, the risk of bleeding will fall significantly **(Thomas and Ziv, 2005).** It follows logically that the pharmacological efforts towards preventing or treating bleeding varices should be based

on agents that can reduce portal to non bleeding levels (or = 12 mmHg).

The medical treatment of portal hypertension has experienced marked progress in the past decade due to the production of effective portal hypertension therapy. The American Association for the Study of Liver Diseases (AASLD) issued guidelines in 2007 for the prevention of variceal recurrent bleeding. The approaches recommended by the guidelines (nonselective beta blockers, endoscopic variceal ligation, transjugular intrahepatic portosystemic shunts, and liver transplantation), as well as other options for the prevention of recurrent variceal bleeding (Garcia-Tsao G, 2007).

Unfortunately, many patients with portal hypertension are not receiving ß-blocker therapy or are not on doses adequate to attain therapeutic results. The reasons include: therapy is never initiated, the dose is not therapeutic, and the patient or the healthcare provider discontinues ß-blockers because of the side effects.

This study was conducted to identify the effect of propranolol as a non selective beta-blocker on portal hypertension using the changes in portal hemodynamics which can be non-invasively visualized and followed up by using duplex Doppler ultrasonography**.**

Another modality used to study liver diseases nowadays is the Doppler technique. Doppler ultrasound and color Doppler are being used routinely in the study of vascular structures of the abdomen, and more particularly the liver. Recent published reports have shown that all patients with hepatic cirrhosis and chronic hepatitis should be studied in the first stage of their illness and in the follow-up by using Doppler techniques **(Martinez – Noguera, 2002).**

In particular many studies have been conducted to evaluate the role of duplex ultrasound in diagnosis of portal hypertension and liver cirrhosis. ***Hassan (2002)*** proved that portal vein diameter and portal vein congestive index were useful parameters for diagnosis of portal hypertension

Baddar (2003) concluded that the use of duplex ultrasonography in measuring the portal vein hemodynamics was a predictive non invasive model for portal hypertension and esophageal varices presence and bleeding in cirrhotic patients, and it also provided a relevant improvement to etiological clinical, biochemical and predictive parameters.

The study conducted by ***Alpay et al. (2005)*** evaluated the value of Doppler ultrasonography in assessing the progression of chronic viral hepatitis and in the diagnosis and grading of cirrhosis. They concluded that Doppler ultrasonography was sensitive to hemodynamic alterations resulting from inflammation and fibrosis, and if sonography was the study of choice to follow the progression of hepatitis, it would not be adequate without Doppler imaging, as Doppler ultrasonography had high diagnostic accuracy in cirrhosis.

Propranolol was one of the earliest drugs used for long-term prevention of rebleeding and prevention of the first variceal bleeding. The results and recommendations for the use of propranolol were controversial. While some reports recommended propranolol for cirrhotic patients with high-risk varices for example, a meta-analysis of 11 trials that included 1,189 patients evaluating nonselective β-blockers (i.e. propranolol) versus non-active treatment or placebo in the prevention of first variceal hemorrhage shows that the risk of first variceal bleeding in patients with large- or medium-sized varices is significantly reduced by β-blockers (30% in controls vs. 14% in β-blocker-treated patients), and indicates that 1 bleeding episode is avoided for every 10 patients treated with β-blockers **(Garcia-Tsao and J. Sanyal et al., 2007)** other could not demonstrate such effect.

Following up the effect of propranolol on heart rate showed that there was a negative correlation between dose of propranolol administered and heart rate, in all groups. Propranolol reduces the force of contraction of heart muscle and thereby lowers blood pressure by reducing the heart rate and the force of muscle contraction **(Baik, 2005).**

In this current study; there was a significant reduction of heart rate with a range of mean 76.8-82.2 beats/min before treatment and 60-79.4 beats/min after propranolol administration in the three studied groups. But the reduction was marked in group III, where the reduction increased by increasing the dose of propranolol (dose of 90 mg/day).In group I with a dose 30 mg/day; heart rate mean value changed from 82.2 to 79.4 beats/min., showing a significant reduction in heart rate.

In group II with a dose 60 mg/day; heart rate mean value changed from 79.5 to 72.2 beats/ min showing a significant decrease.

In group III with a dose 90 mg/day; heart rate mean value changes from 76.8 to 60 beats/ min showing a significant reduction in heart rate.

In the present study there was no significant relation between the severity of liver disease (represented by Child's Pugh classification) and response to propranolol. Where patients were classified as Class A (19, 32%), Class B (34, 57%) and Class C (7, 11%) depending on parameters used for scoring (albumin, bilirubin, encephalopathy, P.T and ascites). After administration of propranolol for one week the score did not change, showing a non significant change. This goes in agreement with several studies **(Bosch, et al., 1984, Garcia-Tsao et al., 1986, El Sahly A.M et al., 1989 and Bendetsen F., 1991).**

However two studies **(Colman, et al., 1982 and Colman, et al., 1984)** showed that increasingly sever liver disease, as indicated by the Child's Pugh classification, was associated with a reciprocal decrease

in responsiveness to propranolol. It was postulated that a near-maximal alpha adrenergic tone was already present in patients with decompensated chronic liver disease, which could have prevented a further reflex increase after propranolol administration, blunting the portal hypotensive effect of the medication **(Colman, et al., 1982).**

Concerning portal vein diameter (PVD); **Zimmerman et al. (2003)** stated that the size of the portal vein diameter greater than 13 mm being 100% specific for portal hypertension. On the other hand, **Piscaglia et al. (2002)** added that despite portal hypertension, the portal vein may remain normal or may even diminish, if it was decompressed effectively by portosystemic shunting, as blood flow is diverted away from it to the opened collateral veins, although it could temporarily enlarge at first because of increasing pressure. This finding was present in 90% of the cases in this current study, in group I; portal vein diameter mean value was 14.6 mm before treatment, and 14.5 mm after treatment. In group II; portal vein diameter mean value was 14.8 mm before treatment and 14.7 mm after treatment. In group III; its mean value was 14.7 mm before treatment and 14.5 mm after treatment.

In groups I and II no significant reduction in portal vein diameter was detected in patients treated with a daily propranolol dose of 30 and 60 mg respectively for one week. Similar findings were found by many authors **(Gaiani, et al., 1991, Cioni, et al., 1992 and Saigal, et al., 1998).**

While there was a slight decrease in portal vein diameter in group III following a propranolol dose of 90 mg daily for one week, but this decrease was non-significant.

As regard portal vein maximum velocity (PVVmax) in group I; it showed a mean value 14.96 cm/sec before treatment and 14.88 cm/sec after treatment. In group II; it showed a mean value 15.26 cm/sec before treatment and 15.18 cm/sec after treatment. In group III; PVVmax, showed a mean value 19.96 cm/sec. before treatment and 19.47 cm/sec. after treatment. Portal vein mean velocity (PVVmean) in group I; showed a mean value 8.7 cm/sec before treatment and 8.64 cm/sec after treatment. In group II; it showed a mean value 8.7 cm/sec before treatment and 8.65 cm/sec after treatment. In group III; PVVmean, showed a mean value 11.37 cm/sec. before treatment and 11.1 cm/sec. after treatment. In groups I and II with a daily dose 30-60 mg/day respectively for one week; there was no significant change in Vmax and Vmean before and after treatment. But; they both decreased significantly in group III after drug administration (90 mg/day for one week).

The portal venous inflow and pressure modulation by propranolol was explored for the first time by **Lebrec *and coworkers (1980)***. They reported that propranolol, at doses which reduced the resting heart rate by 25% (40-180 mg bid), significantly reduced the hepatic venous pressure gradient (HVPG) in 8 patients with well compensated alcoholic cirrhosis, after one month of daily therapy. The same investigators **(Lebrec, et al., 1982)** showed that the HVPG remained significantly lower when measured after 1, 3 and 9 months of therapy. These results were reached also by many other investigators later on **(Burroughs, et al., 1983, Colombo, et al., 1989 and Colman, 1984).**

Regarding the acute response of portal pressure to propranolol, there were variations in the results of different reports. ***Colman et al., (1982)*** found that, despite a significant fall in cardiac output, resting heart rate and mean arterial pressure, oral propranolol did not result in an acute fall in portal venous pressure in patients with alcoholic cirrhosis, portal hypertension and advanced liver disease.

Bosch et al. (1984) investigated the acute effects of propranolol on azygos venous blood flow and hepatic and systemic haemodynamics in 23 cirrhotic patients with portal hypertension. One hour after oral propranolol, in doses that achieved adequate beta-blockade (40-120 mg), a pronounced reduction of blood flow through the gastro-oesophageal collateral system was observed (as evidenced by a highly significant reduction of the azygos venous blood flow of 34%).

In contrast, there were only small changes in the liver blood flow and hepatic venous pressure (13% reduction in hepatic blood flow). It was proposed that the mechanism by which propranolol may reduce the risk of repeated episodes of variceal haemorrhage, in patients with cirrhosis, is related to the reduction in oesophageal collateral blood flow, together with its ability to decrease portal pressure **(Bosch, et al., 1984).**

Comparing those who responded and those who did not in other studies, no significant differences were found in baseline laboratory and haemodynamic parameters, in the severity of liver disease, in the heart rate and blood pressure response to propranolol, or in the propranolol plasma levels achieved two hours after administration.

Regarding the long term effect of propranolol in patients with portal hypertension, the studies of ***Lebrec et al (1980 and 1982)*** are just mentioned. Many other studies reached the same results. ***Rector (1985)*** found that portal pressure fell significantly from 14.5± 3.3 to 12.5± 4.5 mmHg after one week of oral propranolol, with wide variations in the individual response to the drug. ***Vorobioff et al. (1987)*** found in their study that the portal pressure decreased from 21.7 ± 7.2 mmHg to 17.2 ± 5.5 mmHg sixty minutes after oral propranolol in 50% of patients and to 16.1 ± 5.7 mmHg after long term administration (106 ± 35 days) in 70% of patients. Although it is not the method used in this current study; but it proved the therapeutic effect of propranolol on portal hypertension.

A significant difference in the reduction of mean and maximum velocities was detected between group I

and group III and also between group II and group III, while there was no significant difference between group I and group II. Many previous studies had similar results **(Gaiani, et al., 1991 and Cioni, et al., 1992)**

The portal vein cross sectional area (PVCSA) was another parameter evaluated in patients before and after therapy in all groups. Under standard conditions, measurements greater than 13 mm for PVD indicate portal hypertension. In group I its mean value was 1.69 before treatment and 1.67 mm^2 after treatment. In group II its mean value was 1.72 before treatment and 1.7 mm^2 after treatment. In group III its mean value was 1.694 before treatment and 1.657 mm^2 after treatment.

In this study; although the PVCSA decreased in all groups after one week of treatment with propranolol, but the change was non significant. Our findings are in accordance with previous studies which showed that the change in PVCSA on patients treated with propranolol was not significant and PVCSA monitoring could not predict the response to propranolol **(El Sahly, et al., 2001 and Schepke, et al., 2001)**. This goes hand in hand with **Hassan** (***2002***). On the other hand, **Sabba et al**. (***1991***) and **Zironi et al**. (***1992***) stated that in patients with cirrhosis and portal hypertension increased portal vein cross sectional area was consistently reported. The combined increase in portal vein diameter, decrease velocity in portal, splenic and superior mesenteric veins after propranolol therapy suggest a potential role for propranolol in inducing dilatation of the portal veins and consequently relieve in pressure leading to a decrease in the flow velocity in portal vein and its components.

Several studies evaluated the congestion index (CI) as an indicator of portal hypertension in which the ratio of the portal vein cross sectional area (in units of square centimeter) is divided by the mean portal flow velocity (in units of centimeter per second). This ratio reflects the physiologic changes that occur in portal hypertension, i.e., portal vein dilatation associated with diminished flow velocity. In individuals without portal hypertension, the ratio should not exceed 0.07 **(Martins et al., 2000).**

In this current study the portal vein congestion index mean value was 0.202 before treatment and 0.2 cm. sec after treatment, showing non significant change. In group II its mean value was 0.202 before treatment and 0.2 cm. sec after treatment, showing non significant change. In group III its mean value was 0.151 before treatment and 0.149 cm. sec after treatment, showing non significant decrease too.

A study comparing the effect of a combined treatment with propranolol and isosorbide-5-mononitrate versus propranolol alone on Doppler ultrasound parameters in patients with cirrhosis and portal hypertension, revealed relative decrease of the portal vein congestion index in patients received propranolol alone (**Orban Schiopu et al., 2005**). Another study by **El-Sahly et al**. (***2001***) showed significant increase of the portal vein congestion index after therapy and the explanation was that the decrease in the portal vein velocity was greater than that of its diameter. **Merkel et al.,** (***1998***) reported a similar finding.

In this study we found that CI in patients following Child's group B and C higher than that in group A. This goes with **Ansary et al. (2000)**, who found that the CI was significantly higher in Child's group B and C as compared to Child's group A.

Multiple comparisons between each two groups covering the hemodynamic parameters determined by Doppler ultrasonography using delta change for finding the actual difference, concluded that: there was a significant change in Vmax, Vmean and PFV between groups I,III and II,III. While there was a significant change in heart rate between groups I, II and a high significant change between groups I, III and II, III.

Some complaints had been detected in all groups during the current study after drug administration, 17 patients (≈28%) suffered from fatigue, and 7 patients (≈12%) suffered from mild bronchoconstriction that to some extent hindered the continuity of the study.

Re-evaluation of the dose and the role of non-selective ß blocker revealed that propranolol might have some role in reducing the diameter and velocity of portal vein; probably by decreasing the portal hypertension by reducing portal blood flow or intrahepatic vascular resistance irrespective of the cause or severity of cirrhosis.

It has been reported that the optimal dose of propranolol is variable due to racial differences in cardiovascular receptor sensitivity **(Baik, et al., 2005).** Patients may have different levels of sympathetic tone, thus requiring different drug concentrations to achieve adequate beta blockade **(Frishman, 1981).** There is inter-individual variation in the degree of pre-systemic hepatic elimination of propranolol, depending upon the hepatic drug-metabolizing enzyme activity **(Sotaniemi, et al., 1979)**. Ninety to ninety five percent of propranolol bounds to plasma proteins and this may contribute to the variability in the drug concentration in the plasma **(Wener, 1980)**. **Mies et al., (1997)** reported the need of higher doses of propranolol for adequate beta blockade particularly in patients with portal hypertension due to schistosomiasis. There are also non-responders to propranolol in whom the portal pressure exhibits less than 10 % reduction or even increase following an oral dose of 80 mg propranolol (irrespective of heart rate reduction) **(Toubia and Sanyal (2008).**

Commonly used doses of propranolol (30-60mg/day), showed no significant difference on portal hemodynamics. While propranolol in a dose of 90mg/day showed a significant positive change on Vmean, Vmax and PFV. Regarding reduction in heart rate; patients receiving propranolol must be cautiously monitored.

It should be taken into consideration that this study has several limitations. First the small sample size does

not allow drawing sufficient conclusions. The short follow up did not provide proper assessment of the long term effects of propranolol therapy on portal haemodynamics.

Corresponding author
Riham Mohamed Elshafie
Clinical Pharmacy Department, Ain Shams Specialized Hospital.

References:

Abdel-Mageed M., Hosni L. and Mohamed S.K. (2000): Portal-splenic and extrasplanchnic color Doppler haemodynamics in cirrhotic patients. International Congress of Ultrasound and Radiology, 15-17 February, Cairo-Egypt. P: 78.

Albillos A, Penas B, Zamora J. (2010):(Abstract) Role of endoscopy in primary prophylaxis for esophageal variceal bleeding. Clin Liver Disease 14(2): 231-250.

Alpay, H.; Birsen, S.; Çetin, Ç.;et al. (2005): Value of Doppler Sonography in Assessing the Progression of Chronic Viral Hepatitis and in the Diagnosis and Grading of Cirrhosis. J Ultrasound Med; 24:311-321.

Ansary M., Hashem N., El-Ray et al. (2000): portal-splenic haemodynamic changes in patients with chronic liver disease. International Congress of Ultrasound and Radiology, 15-17 February,Cairo-Egypt. P: 89.

Baddar, E. (2003): Portal duplex sonography as a predictive test in patients with oesophageal varices,comparison between bleeders and non bleeders.M.S.Thesis, Dep of Radiology.,Ain Shams University

Baik SK, Jeong PH, Ji SW. (2005): Acute hemodynamic effects of octreotide and terlipressin in patients with cirrhosis: a randomized comparison. Am J Gastroenterol. Mar 2005;100(3):631-5

Bendetsen F., Henriksen J.H., and Sorensen T.L. (1991): propranolol and hymodinamic response in cirrhosis. J. Hepatol., 13 (2): 144-8.

Bosch J., Mastai R., Kravetz D. et al. (1984): Effects of proprabolol on azygoz vebous blood flow, hepatic and systemic haemodynamics in cirrhosos. Hepatology, 4 (6): 1200-5.

Burroughs A.K Jenkins W.J and Sherlock S. (1983): Controlled trial of propranolo for the prevention of recurrent variceal hemorrhage in patients with cirrhosis. N. Eng. J Med., 309:1539.

Cioni G., D' Alimonte P., Zerbinti F. et al. (1992): Duplex-Doppler ultransonography in the evaluation of cirrhotic patients with portal hypertension and in the analysis of their response to drugs. J. Gastroenterol. Hepatol., 7(4): 388-92.

Clifford S. Cho, and Layton F. Rikkers, (2004) : 5 Gastrointestinal tract and abdomen, principles and practice (portal hypertension), (10)1

Colman J., Magnot p. and Dudley p. and duley F. (1984): the Effect of acute and chronic oral propranolol on portal venous pressure Gastroenteteology, 86 (5): 1315.

Colman J. , Jennings G.L. and McLean A.J. (1982): Propranolol in decompensated alcoholic cirrhosis Lancet, 2:1040

Colombo M., De Franchis R., Tommasini M. et al: (1989) B blockade prevents recurrents gastrointestinal bleeding in well-compensated patients with alcoholic cirrhosis: a multicenter randomized controlled trail. Hepatology. 9:433-438.

El Sahly A.M . and Abdel-Latif Z. (2001): Doppler and Endosonographic study of the portal haemodynamics before and after propranolol therapy .

El Sahly A.M . Hantad A.Y., Abdel-Rahman H,M et al. (1989): The effect of propranolol on portal hypertension in patients with schistosomai hepatic fibrosis. Egypt. J Bilh., Vol. 11. No 1-2, p. 123-132.

Eugene R. Schiff, Willis C. Maddrey (2011): Schiff's Disease of the liver: 336

Frishman W. (1981): Clinical pharmacology of the new beta adrenergic blocking drugs. Part 1. Pharmacodynamic and pharmacokinetic properties. Am. Heart J.; 97: 633.

Gaiani S., Bolondi L. Bassi S.L. et al. (1991): Prevalence of hepatofugal portal on portal flow in liver cirrhosis: Clinical and endoscopic correlation in 228 patients. Gastroenterol, 100:160.

Gaiani S., Bolondi L., Fenyves D. et al. (1991a): Effect of propranolol on portosystemic collateral circulation in patients with cirrhosis. Hepatology, 14(5):824-9.

Garcia –Tsao , Laurie D. Deleve, Alexander Zipprich and Roberto J.Grosmann (2011): Vascular liver disease: Mechanisms and management. (6)77

Garcia-Tsao G, Sanyal AJ, Grace ND, et al. (2007) : Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology; 46:922

Garcia-Tsao G. (2001): Current management of the complications of cirrhosis and portal hypertension: variceal hemorrhage, ascites, and spontaneous bacterial peritonitis. Gastroenteology. 120(3):726-48

Garcia-Tsao, G.; Garce, G.; Groszmann, R.J.; et al. (1986): Short-term effects of propranolol on portal venous pressure. Hepatol., 6: 101-107.

Goyal N, Jain N, Rechapalli V et al.,: (Abstract|) (2009): Non-invasive evaluation of liver cirrhosis using ultrasound. Clin. Radiol. 64(11): 1056-66.

Hassan, Y. (2002): Role of coloured duplex sonography in evaluation of portal circulation and grading of liver disease. M.D.Thesis, Dep of Radiology.Ain Shams University.

Lebrec D. Hillon P., Monoz C. et al. (1982): The effect of propranolol on portal hypertension in patients with cieehosis: A haemodynamic study. Hepatology, 2 (5) : 523

Lebrec D, Poynard T, Hillon P, Benhamou JP. (1981): Propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis. N Engl J Med 1981;305:1371-4.

Lebrec D., De Fleury P., Rueff B. et al. (1980): Portal hypertension size of oesophageal varices and risk of gastrointestinal bleeding in alcoholic cirrhosis Gastroenterology,79:1139

Lebrec D., Nouel O., cobric M. and Benhamou J.P (1980): Propranolol; a medical treatment for portal hypertension. Lancet, 2:180.

Martinez - Noguera, A.; Montserrat, E.; Torrubia, S.; et al. (2002): Doppler in hepatic cirrhosis and chronic hepatitis. Semin. Ultrasound CT, MR, 23 (I): 19-36.

Martins, Jacob Szejnfeld, Flávio G. Lima and Angelo Paulo Ferrari (2000): Endoscopic, Ultrasonographic, and US-Doppler Parameters as Indicators of Variceal Bleeding in Patients with Schistosomiasis, Volume 45: 1013-1018.

Merkel M.C., Gatta A., Bolognesi M. et al. (1988): the calcium-channel blocker; verapamil does not lower portal pressure in patients with alcoholic cirrhosis Br. J. Clin. Pharmacol., 26:273.

Mies S., Neto O.B., Beer A. et al (1997): Systemic and hepatic hemodynamics in hepatosplemic Manson's schistosomiasis with and without propranolol. Dig. Dis. Sci., 42 (4): 751-61.

Orban Schiopu, A.M.; Balas, B.I.. and Diculescu, M. (2005): The effect of a combined treatment with propranolol and isosorbide-5-mononitrate on Doppler ultrasound parameters in patients with cirrhosis and portal hypertension. Rom J Gastroenterol. 2005 Jun;14(2):123-130

Rector W.G. (1985): Propranolol for portal hypertension. Arch Intern. Med., 145 : 648.

Piscaglia, F.; Donati, G.; Ceciliani, L.; et al. (2002): Influence of the spleen on portal haemodynamics: a non-invasive study with Doppler ultrasound in chronic liver disease and haematological disorders. Scand J. Gastroenterol; 37 (10): 1220-1227.

Sabba, C.; Weltin, G.G.; Cicchetti, D.V.; et al. (1991): Observer variability in echo-Doppler measurements of portal vein: effect of cooperative training program. Hepatol., 21: 428-33.

Saigal S., Chawla Y. and Dilawari J.B. (1998): Assessment of effects of propranolol on portal hemodynamics in cirrhosis by duplex ultrasonography. Indian J Gastroenterol, 17 (2): 51-2.

Samy A Azer, Julian Katz (2010): Esophageal Varices Treatment and Management (Medsacpe).

Schepke, M.; Raab, P.; Hoppe, A.; et al. (2001): Comparison of portal vein velocity and hepatic venous pressure gradient in assessing the acute portal hemodynamic response to propranolol in patients with cirrhosis. Am. J. Gastroenterol.; 96 (6): 1947

Serag Esmat and Dalia Omran (2011); Study of Noninvasive Predictors of Portal Hypertension in Liver Cirrhotic Egyptian Patients**.** Journal of American Science, 7(1)

Simonetti G. (1999): Diagnostic imaging oi portal system. Gut, 45 (suppl.5) : A57. (abstract).

Sotaniemi E.A., Arittila M., Pelkenen R.o. et al(1979): Plasma clearance of propranolol and satolol and hepatic drugmetabolizing activity. Clin. Pharmacol Ther; 26: 153.

Thomas D. Boyer and Ziv J. Haskal(2005); The Role of Transjugular Intrahepatic Portosystemic Shunt in the Management of Portal Hypertension; HEPATOLOGY, Vol. 41, No. 2:2

Thuluvath P, Krok K. (2005): Noninvasive markers of fibrosis for longitudinal assessment of fibrosis in chronic liver disease: Are they ready for prime time? American Journal of Gastroenterology. 100:1981–1983.

Toubia N, Sanyal A. (2008): Portal hypertension and variceal hemorrhage. Medical Clinics of North America. 92:551–574.

Vorobioff J., Picabea E., Villavicencio R. et al. (1987): Acute and chronic haemodynamic effects of propraholol in unselected cirrhotic patients. Hcpato 7 (4):648.

Wener N. (1980): In Gggdman and Oilman's The Pharmacologic basis of therapeutics. 6th edition. MacMillan Publishing Co., Inc., New York. P. 188.

Wilbur K, Sidhu K. (2005): Beta blocker prophylaxis for patients with variceal hemorrhage. Journal of Clinical Gastroenterology. 39(5):435–440.

Zimmerman, P.; Farooki, S.; David, S.K.; et al. (2003): Doppler sonorgraphy of the hepatic vasculature. Freedom of Information Act Disclaimer. 3 (6): 53-72.

Zironi, G.; Gaiani, S.; Fenyves, D.; et al (1992): Value of measurements of mean portal flow velocity by Doppler flowmetry in the diagnosis of portal hypertension. J.Hepatol; 16 (3): 298.

2/1/2012