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Losartan versus Propranolol in Evaluation of Portal Pressure in Patients with Liver Cirrhosis

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Abstract: *During last decade, increased knowledge of the pathophysiology of portal hypertension (PHT) has resulted in the use of new pharmacological targets; most importantly for the reduction of intrahepatic resistance, which is now recognized to be due in part to activated stellate cell contraction. Orally active angiotensin II receptor antagonists represent a recent therapeutic development in the inhibition of RAAS (renin-angiotensinaldosterone system). Doppler and color coded Doppler sonography studies allow non-invasive visualization of the portal vein. Vein diameter, flow velocity, flow direction, presence or absence of thrombosis and porto-systemic collaterals can be visualized (Schmassann et al., 1993). AIM OF WORK: The aim of this work was to make prospective study to assess Losartan versus Propranolol in evaluation of portal pressure in patients with liver cirrhosis by Doppler Ultrasound. This study was done on sixty patients with liver cirrhosis (38 males and 22 females), their ages ranged between 42 and 62 years. The patients were randomized into one of two groups for evaluation of portal hypertension by doppler ultrasound: (1) Group I, in which, Losartan 50 mg daily was given to them for 3 months and this group included 30 patients; 20 males and 10 females with mean age ranged from 40 to 60 years. (2) Group II, in which, Propranolol 40 mg daily was given to them for 3 months and this group included 30 patients; 18 males and 12 females with mean age ranged from 38 to 58 years. All patients subjected to the following history taking, clinical examination, laboratory evaluation including: complete blood count, liver function tests, urea and serum creatinine, modified Child-Pugh score to assess the degree of hepatic decompensation of the patients, abdominal ultrasonography. Results: The comparison between group1(losartan 50mg\day) and group II(propranolol 40mg\day) after 3 months of treatment showed statistically significant changes as regard grade of esophageal varices, portal hypertensive congestive gastropathy, damping index of hepatic vein wave form, where groupI (Losartan group) after 3 months induced a statistically significant decrease in grade of esophageal varices in 21 (70%) patients (P value 0.001) and disappearance of signs of impending rupture in 5 patients out of 14 patients had these signs before treatment but in group II (Propranolol group) after 3 months showed statistically non-significant decrease in grade of esophageal varices (23.3%) patients (P value 0.065) and disappearance of signs of impending rupture in 4 patients out of 16 patients had these signs before treatment and in group I regarding portal hypertensive congestive gastropathy after 3 months there was a statistically significant decrease in grade of portal hypertensive congestive gastropathy in 10 (66.6%) patients (P value 0.011), on the other hand, in group II after three months of treatment there was a statistically non-significant decrease in grade of portal hypertensive congestive gastropathy only (21.4%) of patients (P value 0.432), as regard to Doppler data of portal pressure in group I (losartan group) after 3 months there was a statistically significant decrease in damping index (P value <0.001), with Paired Differences (0.150 ± 0.064) and groupII after 3 months induced a statistically significant decrease in damping index of hepatic vein wave form (P value <0.001), with Paired Differences (0.071 ± 0.087). Conclusion: we concluded that Losartan in a dose of 50 mg/day orally was more effective than Propranolol 40 mg /day orally in reducing portal pressure via measuring damping index of hepatic wave form, portal vein diameter, portal vein velocity and splenic longitudinal diameter, also losartan was more effective in assessing esophageal variceal grades, portal hypertensive gastropathy and well tolerated than Propranolol.*

I. Introduction

Portal hypertension is a common complication of liver cirrhosis. Cirrhotic patients with PHT develop oesophageal varices and are at very high risk of variceal bleeding (D'Amico et al., 1999). The incidence of oesophageal varices development is approximately 5% per year in patients with cirrhosis, and progression from small to large varices occur in 10% to 20% of cases after 1 year.In the 2 years following the first detection of oesophageal varices, the risk of variceal bleeding ranges between 20% to 30% and result in mortality of 25% to 50% within a week of the first bleeding episode (D'Amico et al., 1986). The frequency of bleeding from large varices is 30-50% compared with 5-18% for small varices (Debernardi-Venon W, 2002). Primary prophylaxis of oesophageal variceal hemorrhage is an important issue in management of PHT (Svoboda P et al., 1992).

Different treatments have been proposed to prevent first variceal bleeding. Surgical portocaval shunts and endoscopic sclerotherapy significantly reduce first variceal bleeding but at the price of increased side effect

and, in some studies, higher mortality. Therefore, they are considered unsuitable. Since PHT reflects elevated splanchnic blood flow and increased intrahepatic vascular resistance, a goal of drug intervention has been to normalize hepatic hemodynamics and reduce vascular resistance. Certain drugs accomplish this by reducing portal blood flow, some by reducing intrahepatic vascular resistance and others by mechanisms that have not been completely clarified(Lebrec,1994). Non-selective β-blockers have proved effective in reducing portal pressure by lowering splanchnic blood flow and are used in primary and secondary prevention of variceal bleeding. However, the mean decrease in portal pressure in response to propranolol is only approximately 15% and one third of cirrhotic patients do not respond despite adequate blockade (Vyas,K., et al., 2002). Despite the fact that β-blockers were the main stay for the primary prevention of variceal bleeding, results of EVL in terms of efficacy and safety are promising. During last decade, increased knowledge of the pathophysiology of PHT has resulted in the use of new pharmacological targets; most importantly for the reduction of intrahepatic resistance, which is now recognized to be due in part to activated stellate cell contraction. Orally active angiotensin II receptor antagonists represent a recent therapeutic development in the inhibition of RAAS (renin-angiotensinaldosterone system) (Burnier and Brunner, 2000). The renin-angiotensin-aldosterone system (RAAS) is usually activated in patients with liver cirrhosis and this represent a haemostatic response to counterbalance the vasodilatation, arterial hypotension and renal hypo perfusion observed in portal hypertension. Plasma renin activity is elevated in cirrhotics and is correlated with the hepatic venous pressure gradient (HVPG) (Vlachogiannakos et al., 2003). Angiotensin II (AT-II) is considered a potential mediator of intrahepatic portal hypertension because its plasma levels are elevated in cirrhosis (Vlachogiannakos et al., 2003). Infusion of AT-II induces a rise in portal pressure (Ballet et al, 2000), nhancement of the adrenergic vasoconstrictor influence on the portal system (Goodfriend et al., 2000), direct contractile influence on activated stellate cells, and sodium and fluid retention induced by stimulation of aldosterone secretion (Pinzani et al., 2001) are possible mechanisms that contribute to the portal hypertensive effect of AT-II. Hence, in theory, blockade of the RAAS by angiotensin converting enzyme (ACE) inhibitors/AT-II receptor antagonists should be beneficial for improvement of fluid and salt secretion and reduce portal pressure in cirrhotic patients. ACE inhibitors block the RAAS preventing the conversion of inactive A-I to active AT-II and may improve portal hypertension. However, concerns have been raised about their safety because of arterial hypotension and deterioration of renal function (Nussberger et al., 2000). The AT-II receptor antagonists Losartan and Irbesartan have been studied in portal hypertensive patients with promising results (Schepke M et al., 2008). Doppler and color coded Doppler sonography studies allow non-invasive visualization of the portal vein. Vein diameter, flow velocity, flow direction, presence or absence of thrombosis and porto-systemic collaterals can be visualized (Schmassann et al., 1993). This work aimed to make prospective study to assess losartan versus propranolol in evaluation of portal pressure in patients with liver cirrhosis by Doppler ultrasound.

Changes in Portal Hypertension and Cirrhosis:

In cases of chronic liver disease, the cross-sectional area of the portal vein trunk becomes greater as the liver injury proceeds (Shiraki et al 1988).The cross-sectional area of the portal vein increase in patients with portal hypertension (0.99cm² in normal subjects and 1.49cm² and 1.56cm² in liver cirrhosis and idiopathic portal hypertension, respectively) (Moriyasu et al., 1986 b).The size of the portal vein may be increase, with a portal vein diameter of > 1.3cm being 100% specific for portal hypertension, though this finding is present in only 75% of cases. The lower sensitivity is likely due to decrease portal vein size as portosystemic collaterals increase (Zimmerman et al., 2003).

Portal Vein Flow Velocity: Nelson et al., (1993) obtained Doppler tracings from portal vein at the point where it enters the liver parenchyma. Image directed Doppler ultrasound is a sufficiently accurate method to measure portal blood flow in cirrhotics (Bolognesi et al., 1995).

Calculation of the mean Velocity (V mean):

There are 2 ways to obtain the mean velocity, either by measuring the peak velocity (V peak) and then calculating the V mean, or by measuring V mean directly by "even insonation ". (a) Measuring the peak velocity (V peak) and calculating V mean: The sample volume is positioned in the center of the vessel and the gate is adjusted so as to eliminate the background [2 mm according to Tincani et al, (1993), 3-6 mm according to Finn et al., (1993) and 5-10 mm according to Schmassmann et al 1993).The velocity measured is the maximum velocity (V peak). V mean is calculated by the software as: V peak obtained, multiplied by a correction factor of 0.57 obtained from an experimental study on circulation model (Moriyasu et al., 1986). However, Ozaki et al., (1988) assumed the velocity profile to be flat within the portal vein (measuring the velocity at any point within the lumen) and admitted that this method might be inaccurate. (b) Measuring V mean directly by Kim MY et al (2009) described the "uniform" or" even insonation" to determine V mean. It consists of utilization of a sample volume corresponding to the vessel diameter (without encountering the vessel wall) to consider also the peripheral component of the flow profile and to have uniform ultrasound intensity. The uniform insonation

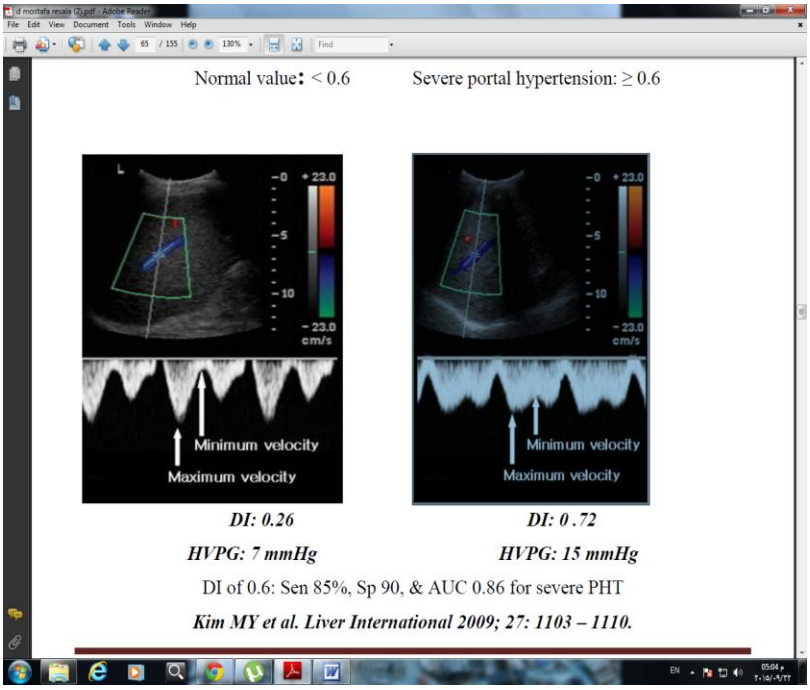
approach is probably the most accurate, but requires purpose-built equipment which is not easily available (Nelson et al., 1993).

Damping Index of HV waveform in cirrhosis:

The ratio between minimum velocity (cm/sec) of downward HV and maximum velocity (cm/sec) of downward HV, as determined by duplex-Doppler system.

Damping index = Minimum velocity of downward HV

Maximum velocity of downward HV



II. Patients And Methods

This was a prospective study done on sixty patients with liver cirrhosis attended to the outpatient clinic and inpatient department of AL-houssien University hospital, Tropical Medicine Department, Al-Azhar University during the period from January to August 2014. The studied patients included 38males and 22females, their age ranged between 42 to 62years.The aim of the study was to evaluate the role of Losartan versus propranolol on portal hypertension in cirrhotic patients by doppler ultrasound. Inclusion criteria: Liver cirrhosis diagnosed by clinical, biochemical and ultrasonographic parameters. Exclusion criteria: Patients with portal vein thrombosis, renal artery stenosis, hyperkalemia, pregnancy, reversible airways disease, particularly asthma or chronic obstructive pulmonary disease (COPD), bradycardia(<60 beats/minute), severe hypotension, atrioventricular block (second or third degree) and shock.

 Patients groups: After an informed consent from patients they were randomly divided into one of two groups for evaluation of portal hypertension by Doppler ultrasound.

GroupI: Losartan 50 mg daily was given to the patients for 3 months,this group included 30 patients; 20 males and 10 females with mean age ranged from 40 to 60years. GroupII: Propranolol 40 mg daily was given to them for 3 months, this group included 30 patients; 18 males and 12 females with mean age ranged from 38 to 58years. All the patients subjected to the following: 1-history taking, 2-clinical examination, 3-laboratory investigations including: complete blood count, liver function tests including (serum bilirubin, albumin, total proteins, SGOT (AST), SGPT (ALT), prothrombin time& concentration and INR), blood urea and serum creatinine, 4-modified Child-Pugh score to assess the degree of hepatic decompensation of the patients, 5-MELD scoring, 6-abdominal ultrasonography to detect the following: criteria suggestive of chronic liver disease and cirrhosis in the form of increased liver echogenicity, loss of homogenous texture to be replaced by speckled, coarse texture, irregular liver margins, attenuation of intrahepatic portal and hepatic veins, relative enlargement of caudate lobe and atrophy of right lobe (ratio of caudate/right lobe in cirrhosis is >0.65)), ascites and it was classified according to its amount into mild (free fluid in the pelvis and in the hepato-renal pouch), moderate (free fluid in the flanks), massive (free fluid in the central part of the abdomen & around the intestine), (Bhathal PS and Grossman HJ, 1985), Portal vein to detect the diameter in mm (Ozaki et al., 1988), Portal vein blood mean velocity in cm/sec (Grant et al., 1992),(e) Hepatic veins flow pattern (Zironi,G, et al 1992), spleen to detect splenic longitudinal dimension (cm): Normally, it measures up to 12-13 cm splenic vein diameter in mm

(Ozaki et al., 1988), the normal SV is usually less than 1.0 cm in diameter (Neugebauer G et al., 1992).(7) Doppler Ultrasound: The ratio between minimum velocity (cm/sec) of downward HV and maximum velocity (cm/sec) of downward HV, as determined by duplex-Doppler system.
Damping index = Minimum velocity of downward HV and Maximum velocity of downward HV, so normal value: < 0.6 and severe portal hypertension: ≥ 0.6

DI of 0.6: Sen. 85%, Sp. 90, & AUC 0.86 for severe PHT (Kim MY et al., 2009), 8-upper endoscopy 9-medical therapy was given to sixty patients assigned into two groups; Losartan group (groupI) which was given 50 mg /day and Propranolol group (groupII) which was given 40 mg/day to be taken daily regardless meals and to take it with food if stomach upset occurs, we advised the patients to take each dose at the same time each day, we instructed the patients not to change the dose or stop taking unless advised by us, we advised the patients to monitor and record Blood Pressure and to inform us if abnormal measurements are noted, we instructed the patients to lie or sit down if they experience dizziness or light headedness when standing, we informed patients that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to excessive fall in Blood Pressure resulting in light headedness or fainting, we advised women to inform us if pregnant, planning to become pregnant, or breastfeeding, we instructed the patients to immediately discontinue drug and notify us if any of the following occured: swelling of the face, lips, eyelids, or tongue, difficulty breathing, or difficulty swallowing and we instructed the patients not to take any medications unless advised by us. 10- follow up schedule: all the patients in both groups were followed up for 3 months by clinical assessment, laboratory investigations, modified Child's score, MELD score, Ultrasonographic evaluation and Doppler assessment (by the same examiner, using the same machine and under the same conditions), endoscopic assessment especially for the grade of varices, signs of impending rupture and grade of portal hypertensive gastropathy.

11- statistical analysis: data have been processed by SPSS (Statistical Package for Science and Society) version 12.0 for Windows XP. The descriptive statistics were presented with mean ± standard deviation (SD) for quantitative variables. All qualitative data were expressed by frequency (number) and percent. Comparisons between groups were done using Chi-Square test, Fischer's Exact test or Mcnemar test when appropriate for qualitative data but independent sample t test and Paired sample t test were used for normally distributed quantitative variables while Non parametric Mann whitnney test and wilcoxon singed ranks test were used for abnormally distributed quantitative variables. In all tests, P value was considered significant if < 0.05.

III. Results

Table (1): Changes in Damping index (DI) for the studied groups pre and 3 months post treatment with Losartan and Propranolol.

Damping index	Before treatment (n = 30)		After treatment (n = 30)		P value
	Mean	SD	Mean	SD	
Losartan 50 mg/day	0.725	0.068	0.574	0.080	<0.001*
Propranolol 40 mg/day	0.744	0.069	0.673	0.115	<0.001*

The mean value showed statistically significant change between pre and 3 months post treatment with Losartan and Propranolol in lowering portal hypertension but losartan more effective than Propranolol.

Table (2): Changes in ultrasonographic assessment of portal vein and spleen diameter for the studied groups pre and 3 months post treatment with Losartan and propranolol.

Losartan 50 mg/day	Before treatment (n = 30)			After treatment (n = 30)			P-value	P-value between Losartan and Inderal
	Mean	±	SD	Mean	±	SD		
Portal vein diameter(mm) Losartan 50 mg/day	13.667	±	1.807	13.267	±	1.574	<0.001	0.106
Portal vein diameter(mm) Propranolol 40 mg/day	12.900	±	1.807	12.667	±	1.647	0.032	
Portal vein velocity (cm/sec.) Losartan 50 mg/day	11.533	±	2.255	12.533	±	1.613	<0.001	0.476
Portal vein velocity (cm/sec.) Propranolol 40 mg/day	11.133	±	2.063	10.733	±	1.795	0.012	
Spleen diameter(cm) Losartan 50 mg/day	15.033	±	1.671	14.500	±	1.253	<0.001	0.052
Spleen diameter(cm)	15.900	±	1.709	15.600	±	1.673	0.010	

Propranolol 40 mg/day								

As regard to Losartan group, there was statistically significant decrease in all studied parameters as regard to portal vein diameter (P value <0.001) and splenic diameter (P value <0.001) but increase in portal vein velocity (P value <0.001) 3 months post treatment, but as regard to Propranolol group, there is statistically significant decrease in all studied parameters were present as regard to portal vein diameter (P value <0.032), portal vein velocity (P value <0.012) and splenic diameter (P value <0.010) 3 months post treatment, the Changes between baseline and 3months post treatment with Losartan and Propranolol as regard sonographic assessment of portal vein and spleen show no statistically significant changes in portal vein, splenic diameter and portal vein velocity 3 months post treatment.

Table (3): Endoscopic assessment of change in the grade of esophageal varices, pre and 3 months post treatment with Losartan and Propranolol.

Grade of Esophageal Varices		Before Treatment (n = 30)	After Treatment (n = 30)	P VALUE
Losartan 50 mg/day	I	0 (0%)	4 (13.3%)	0.001
	II	12 (40%)	19 (63.3%)	
	III	12 (40%)	7 (23.3%)	
	IV	6 (20%)	0 (0%)	
Propranolol 40 mg/day	I	0 (0%)	0 (0%)	0.065
	II	14 (46.6%)	21 (70%)	
	III	16 (53.3%)	9 (30%)	
	IV	0(0%)	0 (0%)	
Varices grade change after 3months:				
Losartan 50 mg/day	Same grade	9	30%	
	Worsened grade	0	0%	
	Improved grade	21	70%	
Propranolol 40 mg/day	Same grade	23	67.6%	
	Worsened grade	0	0%	
	Improved grade	7	23.3%	

As regard Losartan group, there was statistically significant change in the grade of varices (P value 0.001) 3 months post than pretreatment with Losartan, where 21 patients (70%) showed decrease in the grade between pre and 3 months post treatment with Losartan, 6 patients (20%)with grade IV became grade III, 11 patients (36.6%) with grade III became grade II, 4 patients (13.3 %) with grade II became grade I and 9 patients (30%) showed the same grade both pre and 3 months post treatment with Losartan, but as regard to Propranolol group, there was no statistically significant change in the grade of varices (P value 0.065) 3 months post than pretreatment with Inderal, 7 patients (23.3%) showed decrease in the grade pre and 3 months post treatment with Inderal, 7 patients (43.7%) out of 16 patients with grade III became grade II, 23 patients (76.6%) showed the same grade both pre and 3 months post treatment with Inderal, the Changes between baseline and 3months post treatment with Losartan and Propranolol as regard esophageal varices showed that losartan and Propranolol had effect in decreasing the grades of O.V. but Losartan has more effect in decreasing the grades of O.V. than Propranolol.

Table (4): The grade of congestive gastropathy with Losartan and Propranolol.

Congestive Gastropathy		Before Treatment (n = 30)	After Treatment (n = 30)	P VALUE
Losartan 50 mg/day	No	15 (50%)	19 (63.3%)	0.011
	Mild	9 (30%)	11 (36.6%)	
	Severe	6 (20%)	• (0%)	
Propranolol 40 mg/day	No	16 (53.3%)	19 (63.3%)	0.432
	Mild	14(46.6%)	11 (36.6%)	
	Severe	0(0%)	0 (0%)	

As regard to Losartan group, ten (66.6%) patients with congestive gastropathy were improved 3 months post treatment with Losartan out of 15 patients and this was statistically significant (P value 0.011), but

as regard Propranolol group, three (21.4%) patients with congestive gastropathy were improved 3 months post treatment with Inderal out of 14 patients and this was not statistically significant (P value 0.432).

IV. Discussion

PHT is one of the most devastating complications of chronic liver disease. Cirrhotic patients with PHT develop esophageal varices with very high risk of variceal bleeding. The first episode of variceal bleeding makes a crucial turning point in the natural history of the disease, the mortality within the first six weeks of the index variceal bleeding is 3%, (D Amico and Luca, 1999), death often results from associated hepatic failure, renal failure, aspiration, sepsis or encephalopathy. Prevention of first variceal bleeding is undoubtedly one of the most important issues in the management of PHT (D Amico et al, 1999*)*. An understanding of the pathophysiology of portal hypertension is important in a discussion of therapies aimed at reducing portal pressure. Portal pressure is equal to the product of portal venous inflow and resistance to outflow from the portal venous system. Portal venous inflow is controlled by the tone of the mesenteric arterioles. Thus, a decrease in mesenteric arteriolar tone results in increases in portal venous inflow and consequently portal pressure. Normal portal pressure is between 5 and 10 mmHg. (upto date online19.3, 2008). Outflow resistance from the portal system may be considered as two separate resistances in parallel. The first is due to resistance to flow through the portal vein, liver, and hepatic vein; the second is due to resistance to flow through collaterals from the portal system that independently drain into the systemic circulation. (upto date online19.3, 2008).

In patients with cirrhosis, elevated portal pressure results from a combination of increased portal inflow due to splanchnic arteriolar vasodilation, and elevated resistance to outflow through distorted hepatic sinusoids. (upto date online19.3, 2008).

It is now recognized that the increase in resistance to flow within the liver is in part due to intrahepatic vasoconstriction secondary to impaired nitric oxide production within the liver. It is estimated that about 30 percent of the intrahepatic resistance may be reversible and is not due to fixed changes in the vasculature. (upto date online19.3, 2008).

The initial mechanism leading to PHT is an increase in hepatic resistance; later an increase in portal blood flow maintains and exacerbates PHT unless portosystemic collaterals develop. Although morphologic changes in cirrhosis are the most important factors in the increase in hepatic resistance, functional factors lead to increased vascular tone contributing to increased hepatic resistance in cirrhosis. This has a therapeutic relevance since it sets the rationale for the treatment of portal hypertension with vasodilators (Goa KL and Wagstaff AJ 1996; Gonzales, Albraldes et al., 2001).

Increase in AT II level is the result of the activation of RAAS which is commonly evidenced in patients with cirrhosis and has been shown to correlate with PHT. AT II increases hepatic resistance and decreases hepatic blood flow in patients with cirrhosis (Banares et al., 1999).

In this study, Losartan 50 mg/day was used for three months in group I as it is orally active, selective and competitive AT II receptor antagonist, blocks the vasoconstrictor and aldosterone-secreting effects of AT II, increases urinary flow rate and has natriuretic effect. In addition, it may induce a more complete inhibition of the RAAS than ACE inhibitors and less likely to be associated with cough and angioedema (upto date online16.1, 2008).

Propranolol 40 mg/day was used in group II as it is orally non-selective β blocker blocks the adrenergic dilatory tone in mesenteric arterioles resulting in unopposed alpha adrenergic mediated vasoconstriction and therefore a decrease in portal inflow. However, the report of increased mortality rates in patients with refractory ascites who received nonselective beta blockers has called their safety into question (upto date online16.1, 2008).

We used doppler ultrasound for evaluation of changes in portal pressure as it is a safe, painless and non-invasive procedure compared with HVWP (Feu et al., 1995; Goldberg, 1997; Gebel, 1999). Despite the errors due to measurements, many authors agree that doppler sonography is suitable for monitoring of the changes induced by medical treatment (Lebrec et al., 1981; Gaiani et al., 1991; Goldberg, 1997; Gebel, 1999).

Ideally, PHT should be evaluated by actually measuring portal pressure. HVPG measurement is a safe and reproducible procedure. However, at present, HVPG measurement is not applicable on a routine basis; therefore, alternative methods must be used. Damping index, which is far more widely available than HVPG measurement, is a suitable method, since it is safe, non-invasive and applicable with sensitivity 76% and specificity 82% (Kim MY et al., Liver International, 2009).

As regard to sonographic data of PV and spleen in groupI after three months of treatment, there was a statistically significant decrease in splenic longitudinal diameter (P value 0.001), PV diameter (P value <0.001). Also, there was statistically significant increase in PV velocity (P value 0.001) as shown in table 2, the increase of PV velocity after Losartan treatment in our patients may be due to decrease of hepatic resistance as a consequence of the drug effect as an antagonist of the AT II receptors, this was similar to what was reported by Wagatsuma et al.,(2006), in a study to evaluate effect of Losartan on 16 portal hypertensive gastropathy

patients, reported that the mean PV velocity increased significantly, while the PV CI decreased significantly in cirrhotic patients treated with Losartan for 4 weeks. Also Heller J, et al. (2003), in a study on 17 patients to evaluate the effects of losartan, when used alone and when combined with somatostatin, on portal and renal hemodynamics, found a significant increase in PV velocity and PVF 120 and 240 minutes after 25 mg of Losartan. These conflicting results could not be explained from our data and requires further investigation.

As regard to sonographic data of PV and spleen in the group II after three moths of treatment there were a statistically significant decrease in splenic longitudinal diameter (P value 0.010), PV diameter (P value <0.032) and PV velocity (P value 0.012) as shown in table 12.

The decrease of PV velocity after Propranolol treatment may be due to decreased splanchnic blood flow which was promoted by splanchnic vasoconstriction through blockade of β_1 and β_2 receptors as well as reducing cardiac output. Blockade of the β_1 receptors lead to reflex splanchnic vasoconstriction mediated through α_1 receptors and reduction in heart rate, whereas blocking β_2 receptors prevents splanchnic vasodilation (Krige JE, et al., 2001) and (Schepke M, et al., (2008). This was similar to what was reported by Orban Schiopu et al., (2005) in a study to evaluate effect of propranolol on portal hypertension, the authors found that PV velocity decrease with 10%.

The comparison between group I and group II after 3 months of treatment showed that the changes between baseline and 3months post treatment with Losartan and Propranolol as regard sonographic assessment of portal vein and spleen did not show statistically significant changes in portal vein, splenic vein diameter and portal vein velocity.

In this study, Losartan after 3 months induced a statistically significant decrease in grade of esophageal varices in 21 (70%) patients (P value 0.001) and disappearance of signs of impending rupture in 5 patients of 14 patients having these signs before treatment as shown in table 3. Previous studies assessed the effect of Losartan on HVPG not the grade of esophageal varices. It has been shown that changes in HVPG are usually accompanied with parallel variation in variceal size (Gonzales, Albraldes et al., 2001). It was found that 25 mg Losartan given orally to cirrhotic patients for one week induced a significant reduction of the HVPG values. In group II, Propranolol after 3 months induced a statistically non-significant decrease in grade of esophageal varices in 7 (23.3%) patients (P value 0.065) and disappearance of signs of impending rupture in 4 patients of 16 patients having these signs before treatment as shown in table 3. The comparison between group I and group II after 3 months of treatment with losartan 50mg\day and propranolol 40mg\day showed changes between baseline and 3months post treatment with Losartan and Propranolol as regard esophageal varices where Losartan and Propranolol have effect in decreasing the grades of O.V. but, Losartan (P value 0.001) has more effect in decreasing the grades of O.V. than Propranolol (P value 0.065) as shown in table 3. In groupI regarding portal hypertensive congestive gastropathy, Losartan after 3 months induced a statistically significant decrease in grade of portal hypertensive congestive gastropathy in 10 (66.6%) patients (P value 0.011) as shown in table 4. Wagatsuma et al., (2006) reported that portal hypertensive gastropathy improved in 5 (83%) patients out of 6 cirrhotic patients taking Losartan 50 mg for 4 weeks. Although, this percentage is higher than that found in our study, but Wagatsuma et al., (2006) carried out his trial on only 6 patients. In group II regarding portal hypertensive congestive gastropathy, Propranolol after 3 months induced a statistically non-significant decrease in grade of portal hypertensive congestive gastropathy in 3 (21.4%) patients (P value 0.432) as shown in table 4. The comparison between groupI and groupII after 3 months of treatment with losartan 50mg\day and propranolol 40mg\day showed that Losartan (P value 0.011) has more effect in decreasing the grades of portal hypertensive gastropathy than Propranolol (P value 0.432) which has no effect on portal hypertensive gastropathy as shown in table 4. As regard to Doppler data of portal pressure in group I, Losartan after 3 months induced a statistically significant decrease in damping index (P value <0.001), with Paired Differences (0.150 ± 0.064) as shown in table 1. In literature, no studies evaluated the effect of Losartan on this laboratory data. As regard to Doppler data of portal pressure in group II, Propranolol after 3 months induced a statistically significant decrease in damping index of hepatic vein wave form (P value <0.001), with Paired Differences (0.071 ± 0.087) as shown in table 10, this was similar to what was reported by (Moon Young Kim: et al., 13 JUN., 2007).

The comparison between group I and group II after 3 months of treatment with Losartan 50mg\day and Propranolol 40mg\day showed statistically significant change between pre and 3 months post treatment with Losartan and Propranolol in lowering portal hypertension but Losartan more effective than Propranolol as shown in table 1.

Reichen in (1990) reported that β blockers caused a decrease in splanchnic blood flow which was promoted by splanchnic vasoconstriction and reduction of cardiac output. The authors recommended the use of non-selective β blockers for the treatment of portal hypertension.

El-Tourabi et al., (1994) studied the effect of oral Propranolol 160 mg/day for 24 months on portal pressure, in patients with liver cirrhosis and portal hypertension. It was concluded that propranolol reduced mortality as it reduced the occurrence of bleeding from esophageal varices. It was reported that patients whose

portal pressure was reduced by 30% with the use of propranolol would not undergo surgical treatment for portal hypertension. Moreover, the authors recommended that treatment of portal hypertension would consist of the chronic use of propranolol, associated with sclerosis of esophageal varices (Mies S., 1980).

It was reported that Propranolol significantly reduced the occurrence of the first episode of esophageal variceal bleeding in patients with liver cirrhosis (Lebrec, 1994. Merkel et al., 1996), reported that the use of non-selective β blockers is currently recommended for patients with liver cirrhosis and esophageal varices that are at risk of bleeding.

Non selective β blockers (propranolol), reduce portal pressure through both local and systemic effects. In splanchnic circulation, blockade of the vasodilating β_2 adrenoceptors results in unrestricted α-adrenergic activity splanchnic arteriolar vasoconstriction, and decrease portal venous inflow (Mastai et al., 1987). Blockade of the cardiac β_2 receptors decreases the heart rate and cardiac output and secondarily decreases portal venous inflow.

Regarding the tolerability and adverse effects of Losartan and Propranolol in this study, patients in Losartan group tolerated it without significant fall in the MAP and without deterioration of renal function. Nearly similar results were found by Schepke M etal., (2008), where statistically significant mild decrease in MAP without deterioration in renal functions occurs with Losartan in cirrhotic patients. As regards mortality in Losartan and Propranolol group in this study, there were no patients died within the course of the study.

Finally, we concluded that Losartan in a dose of 50 mg/day orally was more effective than Propranolol 40 mg /day orally in reducing portal pressure via measuring damping index of hepatic wave form, portal vein diameter, portal vein velocity and splenic longitudinal diameter. Also losartan was more effective in controlling esophageal variceal grades, portal hypertensive gastropathy and well tolerated than Propranolol.

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