EFFECT OF NON-SELECTIVE BETA BLOCKERS ON ESOPHAGEAL VARICES AND PORTAL VEIN DIAMETER IN CIRRHOTIC HCV PATIENTS

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ABSTRACT

Background: Esophageal varices is one of the major complications of portal hypertension and one of the main causes of death in cirrhotic patients, so prophylaxis from esophageal varices bleeding can decrease the number of deaths in those patients.

Aim of the work: To assess the effect of non-selective beta blockers on portal vein diameter and grades of esophageal varices.

Subjects and methods: Our study was carried out at Gastroenterology and Hepatology unit, Internal Medicine department, Zagazig University hospital. Forty patients with HCV positive liver cirrhosis were enclosed in the study. All were Child Pugh grade A and B, diagnosed by clinical examination, laboratory investigations (hepatitis C virus antibody, hepatitis C virus RNA by polymerase chain reaction, hepatitis B virus surface antigen, liver and kidney functions, complete blood count, INR and alpha feto-protein) and pelvi-abdominal ultrasound findings. Upper gastro-intestinal (GI) endoscopy was done at the beginning of the study for detection and grading of esophageal varices (EVs) and those without EVs were excluded, also portal vein diameter (PVD) was recorded by ultrasound. The maximum tolerated dose of Propranolol (decrease pulse rate by 25% but not below 60 beats per minute) was given to all patients for three months. EVs grading, by upper GI endoscopy, and PVD were reassessed at the end of the study.

Results: Propranolol showed a significant reduction in heart rate and PVD for the pre and post-treatment results after three months of treatment ($P<0.001$ for both). The dose of Propranolol didn't show significant effect on reduction of small size EVs ($P=0.07$) while the percent of reduction of PVD correlated significantly with percent of reduction in EVs grade for the pre and post-treatment ($P<0.05$). A cut off point for detection of significant EVs (GII and III) was 12.5 mm with sensitivity 82.4%, specificity 47.8%, positive predictive value (PPV) 53.8% and negative predictive value (NPV) 78.6%.

Conclusion: Non-selective beta blocker (Propranolol) caused significant reduction in portal vein diameter and the percentage of reduction of portal vein diameter significantly correlated with change in esophageal varices grades.

Key words: Portal hypertension, HCV, Esophageal varices, Portal vein diameter, liver cirrhosis and Non-selective beta blockers.

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INTRODUCTION

Portal hypertension is caused by increase in resistance, blood flow or both of the portal circulation and worsens if portal collateral blood flow increases. In case of cirrhosis the resistance often occurs within the liver, but it can be also pre or post-hepatic**.** Portal hypertension is usually asymptomatic till complications develop **[1].** Liver cirrhosis and schistosomiasis are the most common causes of portal hypertension. Eighty to ninety percent of asymptomatic cirrhotic patients have elevated hepatic venous pressure gradient (HVPG), 40% of them have esophageal varices (EV). From the rest, 6% per year will develop varices **[2].** Most of

clinical manifestations of portal hypertension are related to the primary cause of the portal hypertension (eg, spider angiomata in case of cirrhosis) **[3].** Its complications include splenomegaly, thrombocytopenia, ascites, portal hypertensive gastropathy, variceal hemorrhage and spontaneous bacterial peritonitis. Other less frequent complications are; hepatorenal syndrome, hepatopulmonary syndrome, hepatic hydrothorax and porto-pulmonary hypertension **[1].**

It can be diagnosed by increasing hepatic venous pressure gradient (HVPG) more than 5 mmHg **[1].** As the HVPG increases, the risk of developing complications of portal hypertension and mortality increases **[5].**

The definite way to diagnose portal hypertension is measuring HVPG or upper gastrointestinal (GI) endoscopy to assess the presence of esophageal varices (EVs) and both are considered minimally invasive procedure **[6].**

It is difficult to treat portal hypertension unless treatment of underlying cause. Portal venous pressure can be reduced by non-selective beta blockers (NSBBs) and also by creating an anastomosis between portal and hepatic veins by using shunt procerures (eg, Trans-jagular intrahepatic porto-systemic shunt) **[7].**

As EVs bleeding has a high morbidity and mortality, primary prevention of bleeding is the main concern in the management of portal hypertension. Non-selective beta-blockers such as propranolol and nadolol block the adrenergic dilatation of mesenteric arterioles and reduce portal venous inflow **[8].**

Both NSBBs and esophageal varices ligation (EVL) can be used in prevention of first variceal hemorrhage in patients with medium to large-sized varices and the choice should be based on local resources, patient characteristics and expertise. NSBBs are not indicated, for patients with no varices, to prevent the formation of varices. Patients who have low grade varices with red wale marks carry an increased risk of bleeding, so treatment with NSBB is advised, while those with low grade varices with no signs of increased risk of bleeding may be treated with NSBB to prevent bleeding **[8],** however, it is not advised for patients with refractory ascites and those with Child Pugh C **[9].** NSBBs have other advantages if compared to EVL, such as prevention of bleeding from other portal hypertension sources (portal hypertensive gastropathy and gastric varices) and a possible reduction in the incidence of spontaneous bacterial peritonitis (SBP) **[10].**

AIM OF THE WORK

To assess the effect of non-selective beta blockers on portal vein diameter and grades of esophageal varices.

PATIENTS AND METHODS

I. Patients

Forty patients were involved in the study aged from 21-60 years with a mean±SD of 42.55±12.35 years (41.07±13.69 years in males and 45.9±7.76 years in females). Twenty eight (70%) were males and 12 (30%) were female. All had HCV positive liver cirrhosis. Twenty nine were Child Pugh A (72.5%) and 11 were Child Pugh B (27.5%). Body mass index (BMI) ranged from 21–34.3 with a mean±SD 28.03±3.02 (27.5±2.94 in males and 29.5±3.21 in females).

Inclusion criteria: Patients with liver cirrhosis and HCV diagnosed by positive antibodies and HCV RNA by polymerase chain reaction (PCR), Child-Pugh grade; A or B liver cirrhosis, presence of EVs by upper GI endoscopy with or without evidence of portal hypertension (increased PVD in abdominal ultrasound).

Exclusion criteria: Patients with HBV or other causes of liver cirrhosis, patients with hepatocellular carcinoma, portal vein thrombosis, Child Pugh C, history of variceal sclerotherapy or band ligation, contraindication for beta blockers, patients on beta blockers or any drugs that affects portal vein pressure.

II. Methods

After getting a written informed consent from all patients they were asked to undergo; full history taking and full physical examination, then pelvi-abdominal ultrasound and laboratory investigations (complete blood count, liver and kidney functions, INR, HCV antibodies, detection of HCV DNA by polymerase chain reaction, HBsAg and Alpha-feto protein) were done.

The maximum tolerated dose of NSBBs (Propranolol), decrease pulse rate by 25%, but not <60 beats per minute **[11]**, were given to all patients for three months, then all the work up that was done at the beginning of the study were repeated.

STATISTICAL ANALYSIS

All data were statistically assembled in mean ± standard deviation (SD) (in normally distributed data), range and median (in skewed data distribution), or percentages and frequencies if available. Numerical variables were compared between the studied Groups using Mann Whitney (U) test for independent samples when comparing 2 Groups. When comparing more than 2 Groups, Kruskal Wallis test was used. To represent the accuracy of tests, sensitivity and specificity were used. We used receiver operator characteristic (ROC) analysis to detect the best cut off value for the studied variables. To define the significant independent predictors for the presence, grade of EVs and occurrence of significant EVs, univariate and multivariate regression models were made. P values <0.05 was considered statistically significant. The computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 18.0 for Microsoft Windows was used for all statistical calculations.

RESULTS

The mean±SD of portal vein diameter (PVD) at the pre-treatment results was 12.8±1.34 mm, while the post treatment was 11.4±1.93 mm (P<0.001). As regard the gender, the mean±SD of PVD in females was 12.66±1.49 mm while in males it was 12.8±1.27 mm (P=0.09). There was positive significant correlation between PVD and the age of the patients (P<0.05), but there wasn't any significant correlation between BMI and PVD.

At the pre-treatment endoscopic evaluation of the studied group there was 23 patients (57.5%) had grade I (GI) EVs, 16 patients (40%) had GII and only one patient (2.5%) had GIII EVs, while at the post treatment evaluation 5 patients (12.5%) had no EVs, 24 patients (60%) had GI, 7 patients (17.5%) had GII and 4 patients (10%) hag GIII EVs (P=0.07).

The mean daily dose of NSBBs (Propranolol) used was 66.95±17 mg which caused a significant reduction in the mean of pulse rate from; 79.05±9.02, pre-treatment, to 61.15±4.73, post-treatment (P value <0.001). The maximum percentage of reduction in PVD was 14.35% and was seen with Propranolol dose 60 mg/day

There was significant difference in the mean±SD of PVD for small (GI) EVs 12.1±1.08 mm and significant (GII and III) EVs 13.5±1.28 mm at the pre-treatment evaluation (P<0.001), while the post-treatment evaluation showed 10.2±2.48 mm for G0 EVs, 11±1.74 mm for GI and 12.6±1.43 mm for GII and III (P<0.01). There was a positive significant correlation between percent of change of PVD and EVs grade (r=0.33 and P<0.05).

There was significant correlation between Propranolol dose and PVD at the pre-treatment results (P=0.02), while correlation was very highly significant between EVs grade and PVD at the pre and post-treatment results (P<0.001 and 0.007 respectively).

Table (1): Demographic and clinical data of the studied group:

Variable		(n=40)	
Age (Years)	*Mean ± SD*	42.55 ± 12.35	
	Range	21 - 60	
Variable		**No**	**%**
Sex (M\F)	*Female*	12	30
	Male	28	70
Smoking	*No*	22	55
	Yes	18	45
Hypertension	*Yes*	6	15
Diabetes mellitus	*Yes*	9	22.3
BMI (%)	*Mean ± SD*	28.03±3.02	
	Range	21 – 34.3	

Table (2): Laboratory investigation among the studied groups pre and post treatment:

Variable		Pre (*n*=40)	Post (*n*=40)	Paired tests	p
WBCs/ccm	*Median (Range)*	5.25 (2.2 – 13)	4.95 (2.2 – 11.8)	W 0.29	0.77 NS
Hb *(gm/dl)*	*Mean ± SD* *Range*	12.1 ± 1.84 8.9 – 16.7	11.86 ± 1.6 9 - 15	t 1.52	0.14 NS
Platelets*10^3/ccm	*Median (Range)*	109.5 (33-350)	101.5 (35 – 333)	W 0.64	0.53 NS
Creatinin *(mg/dl)*	*Mean ± SD* *Range*	0.94 ± 0.15 0.6 – 1.3	0.97 ± 0.12 0.6 – 1.4	t 1.51	0.14 NS
T. Bilirubin *(mg/dl)*	*Median (Range)*	1.3 (0.9 – 3.1)	1.3 (0.9 – 3.5)	W 0.44	0.66 NS
D. Bilirubin *(mg/dl)*	*Median (Range)*	0.6 (0.2 – 1.3)	0.5 (0.3 – 1.1)	**W** **2.16**	**0.03***
T. Protein *(g/dl)*	*Mean ± SD* *Range*	5.95 ± 0.73 4.9 – 7.2	5.84 ± 0.53 4.5 – 6.6	**t** **2.03**	**0.04***
Albumin *(g/dl)*	*Mean ± SD* *Range*	3.34 ± 0.55 2.2 – 4.5	3.33 ± 0.52 2.1 - 4	t 0.18	0.86 NS
ALT *(IU/L)*	*Median (Range)*	50 (20 – 144)	40 (13 – 98)	**W** **3.89**	**<0.001****
AST *(IU/L)*	*Median (Range)*	52 (15 – 160)	39 (12 – 102)	**W** **3.92**	**<0.001****
AFP *(IU/L)*	*Mean ± SD* *Median (Range)*	10.43 ± 7.24 10.95 (2 – 34)	----------	------	------- -
INR	*Mean ± SD* *Range*	1.33 ± 0.31 0.9 – 2	1.32 ± 0.31 0.9 – 2.3	t 0.34	0.74 NS

(*) P<0.01 high significant difference.
(**) P<0.001 very high significant difference.
(NS) nonsignificant difference
(W) Wilcoxon signed rank test.
(t) Paired t test
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Table (3): PVD, EVs grade and Child Pugh score among the studied group pre and post-treatment :

Variable	Pre (*n*=40)		Post (*n*=40)		Test of significance	p
PVD: *(mm)*					**t**	
Mean ± SD	12.8 ± 1.34		11.44 ± 1.93		**5.87**	**<0.001****
Range	10 – 15		7 - 15			
Variable	**No**	**%**	**No**	**%**	**Mc Nemar's**	**P**
Esophageal Varices grades:						
No						
G I	0	0	5	12.5	**1.789**	**0.07**
G II	23	57.5	24	60		**(NS)**
G III	16	40	7	17.5		
	1	2.5	4	10		
Child Pugh score:						
A5	20	50	16	40		
A6	9	22.5	13	32.5		
B7	3	7.5	4	10		
B8	6	15	5	12.5	**13.23**	**0.03***
B9	2	5	1	2.5		
C11	0	0	1	2.5		

(*) P<0.05 high significant reduction.
(**) P<0.001 very high significant difference.
(NS) nonsignificant difference.
(t) Paired t test.

Table (4): Pulse rate among the studied group pre and post treatment, dose of Beta blockers used and Correlation between percent of change of PVD and EVs grade:

Variable	Pre (*n*=40)	Post (*n*=40)	Paired t	P
Pulse rate: (beats/min)				
Mean ± SD	79.05 ± 9.02	61.15 ± 4.73	**17.04**	**<0.001****
Range	60 – 95	54 - 71		
NSBB: (mg)		**66.95 ± 17**		
Mean ± SD		**30 – 80**		
Range				

Variable	% of change PVD (*n*=40)	
	r	**P**
% of change in Esophageal varices grade	**0.33**	**<0.05***

(*) P<0.05 high significant reduction.
(**) P<0.001 very high significant difference.

Table (5): Mean of portal vein diameter in relation to esophageal varices, pre and post-treatment:

Variable		Esophageal varices			Test of sig.	P value
		Grade II,III	Grade I	Grade 0		
Pre-treatment						
PV diameter (mm)	Mean±SD	13.5± 1.28	12.21±1.08	---	t 3.91	<0.001**
	Range	10 – 15	10 – 14	---		
Post-treatment						
PV diameter (mm)	Mean±SD	12.6±1.43	11±1.74	10.2±2.48	F 4.45	0.01*
	Range	11 - 15	7 – 4	8 - 14		

(t) Paired t test.
(*) P<0.05 significant difference.
(**) P<0.001 very high significant difference.

Table (6): The cutoff point of portal vein diameter and its validity in diagnosis of esophageal varices pre and post-treatment:

Pre-treatment

P. V. D. *(mm)*	Esophageal Varices Grades		Total
	Grade II, III	Grade I	
>12.5	14	12	26
≤12.5	3	11	14
Total	17	23	40

Test	Sensitivity	Specificity	PPV	NPV	Kappa	P
PV>12.5 mm	82.4	47.8	53.8	78.6	0.28	0.04*

Post-treatment

P. V. D. *(mm)*	Esophageal Varices Grades		Total
	Grade II, III	Grade I	
>11.5	8	9	19
≤11.5	3	15	16
Total	11	24	35

Test	Sensitivity %	Specificity %	PPV %	NPV %	Kappa %	P
PV>11.5 Mm	72.7	62.5	47.1	83.3	0.31	<0.05*

(*) P<0.05 significant difference.

Table (7): Correlation between portal vein diameter, Beta blockers dose and esophageal varices grades pre and post-treatment

Pre-treatment				
Variable	**PVD (*n*=40)**		**BB dose (n=40)**	
	r	**P**	**r**	**P**
BB dose	**-0.33**	**0.02***	---	----
OV grade	**0.54**	**<0.001****	-0.17	0.28 NS
Post-treatment				
BB dose	-0.02	0.90 NS	---	---
OV grade	**0.42**	**0.007***	-0.19	0.25 NS

DISCUSSION

The maximum tolerated dose of Propranolol used at the study, that achieved a 25% reduction in pulse rate but not below 60 bests per minute, ranged from 30 to 80 mg per day (mean± SD of 66.96±17) this dose differ from the dose of the study done by *Pimenta* et al they used a dose 1 – 3.1 mg\kg\day, however the median age in their study was 7.9 years old and the patients were having different etiologies for cirrhosis which may have an effect on the dose used **[12].**

There was a very high significant reduction in the pre-treatment heart rate which ranged from 60 to 95 (mean±SD of 79.05±9.02), while the post-treatment showed a range of 54 to 71 (mean±SD 61.15±4.73) (P<0.001)**.** Our maximum percentage of reduction (-14.35%) was less than that of the study done by *Groszmann* et al, which was 17%, but they used Timolo instead of Propranolol and also the sample size was larger (213 patients) **[13].**

There was a very high significant decrease in portal vein diameter (P<0.001) between the pre and post-treatment (mean± SD was 12.8±1.34 and 11.4±1.93 mm respectively)**.** This result was nearly the same as the study done by *Groszmann et al*, in the effect of beta blockers on the portal vein pressure as they obtain a P value of 0.07 but they used the hepatic venous pressure gradient instead of portal vein diameter and used Timolol instead of Propranolol **[13].**

As a noninvasive predictor for significant EVs, portal vein diameter was a weak test as we found, according to our results, at the pretreatment results that 12.5 mm can be used as a cutoff point for prediction of significant EVs with sensitivity 82%, specificity 47.8%. The post treatment results showed a cutoff value 11.5 mm with sensitivity 72.7%, specificity 62.5%**.** In another study done by *Schepis* and his colleagues, they found that 13 mm PVD is a cut off point for presence of EVs **[14].**

As regard the effect of NSBBs of the EVs size we got nearly the same results as Calés et al. in our study there was a non-significant difference in the EVs grade regarding the pre and post-treatment results and there was also a non-significant correlation between the dose of NSBBs and the percent of reduction of EVs size, while Calés et al found that 31% of patients on Propranolol developed large EVs while the percentage was only 17% in the placebo group **[15].** Those results was different from that of Feu et al, as they found a reduction in HVPG by 20% in after propranolol therapy, but apart from the HVPG they used for assessment of portal hypertension, their study was done over 28 months and that may be the cause of difference **[16]**. Our results was also not the same as Merkel et al, as they found that the cumulative risk for developing large varices was 20% in beta blockers group versus 51% in placebo group (P < 0.001), but they used Nadolol and those results was after 5 years treatment and follow up **[17]**.

CONCLUSION

Non-selective beta blocker (Propranolol) caused significant reduction in portal vein diameter and the percentage of

reduction of portal vein diameter significantly correlated with change in esophageal varices grades

RECOMMENDATION

Non-selective beta blocker (Propranolol) can be used in reduction of portal vein pressure and consequently the grades of esophageal varices.

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