Does Atorvastatin has Adding Effect to Propranolol in Control of Portal Hemodynamics in Patients with Liver Cirrhosis

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Background and study aim: Portal hypertension is abnormal increase in portal pressure. Vasoreactivity, vascular remodeling, and hepatic fibrosis contribute to increased intrahepatic resistance. β blockers decrease cardiac output and mediate splanchnic vasoconstriction. Statins have antioxidant, antiproliferative, and anti-inflammatory properties. We aimed to assess portal vein pressure using Doppler ultrasound in cirrhotic patients before and after atorvastatin administration.

Patients and Methods: This study was conducted on 58 patients Randomized controlled study was done at the hepatology gastroenterology and infectious diseases department of Kafrelsheikh University Hospital on 40 cirrhotic patients who were randomly assigned to either: **Group A**: included 20 cirrhotic patients who were administered 20 mg of atorvastatin and 40 mg of propranolol daily for two months (n=20) or **Group B**: patients who received 40 mg of propranolol alone daily for two months (n=20). Clinical and laboratory evaluation, abdominal Doppler ultrasound and upper endoscopy was done at the start and after two months.

Results: There was a significant difference in portal vein diameter before and after treatment (P-value = .039). Portal vein velocity, portal vein flow volume, hepatic artery resistance index, and hepatic artery pulsatility index showed significant difference between both groups. There was a significant difference in endoscopic grading before and after treatment (P value = .000).

Conclusion: For lowering portal hypertension, atorvastatin and propranolol is more effective than propranolol alone .

INTRODUCTION

Portal hypertension (PHT) is a central cause of hospital admissions and morbidity. The role of sinusoidal endothelial modulating the development of intrahepatic resistance and gastroesophageal varices. Endothelial dysfunction due to hepatic injury leads to a reduction in the production of vasoconstrictors from endothelial cells. Also, hepatic satellite cell contraction and matrix deposition increase intrahepatic resistance **[1-6]**. The prognosis of liver cirrhosis improved with a significant decrease in portal pressure **[7]**. The main therapy for portal hypertension (PHT) is nonselective beta blockers (NSBBs), such as propranolol, which can decrease the incidence of recurrent variceal hemorrhage when used in conjunction with endoscopic ligation. Patients who cannot tolerate β-blockers or have contraindications. The addition of other drugs, such as statins or isosorbide-5 mononitrate, may help in reducing vascular resistance **[9,10]**. Statins decrease the activation of hepatic stellate cells. Statins also have anti-inflammatory, antioxidant, and immunomodulatory effects **[11]**. Atorvastatin may be an effective therapeutic agent for PHT. It has a beneficial antifibrotic effect and enhance hepatic cell function [12-16]. However, in advanced cirrhosis,

organic nitrates (e.g., nonselective NO donors) increase peripheral vasodilatation, leading to a decrease in arterial pressure, and sympathetic system stimulation **[17]**.

Many studies suggest that statins reduce vascular resistance and enhance vasodilatation of the hepatic vasculature. These effects is due to increase of NO in the liver vessels **[18,19]**. Doppler ultrasound, in addition to upper endoscopy, is a non-invasive method to assess blood flow inside portal veins **[19]**.

Aims:

Our aim was to evaluate the benefits of adding atorvastatin to propranolol to decrease portal pressure and consequently decrease variceal size as assessed by Doppler ultrasound and upper endoscopy.

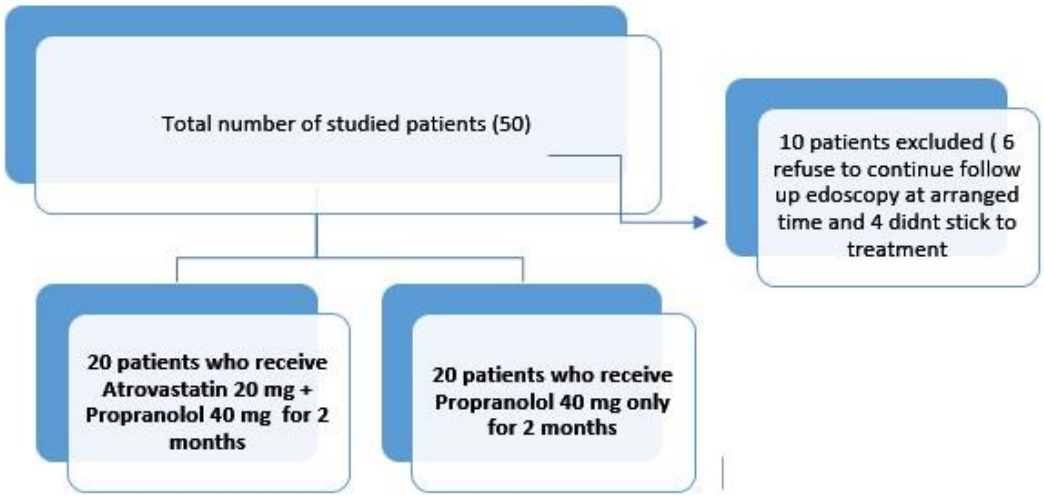
Patients AND METHODS

Type and site of the study: This randomized controlled study was done in the, Hepatology, Gastroenterology and infectious disease department in collaboration with the radiological department at Kafrelsheikh University Hospital.

Patient selection

We included forty cirrhotic patients with PHT from September 2019 to September 2020. Patients were randomized by use of a computer generated random sequence into two groups: **Group A** cirrhotic patients who administered 20 mg of atorvastatin and 40 mg of propranolol daily for two months (n=20); (and) **Group B:included 20 cirrhotic** Patient who received 40 mg of propranolol daily alone for two months (n=20) **(Figure 1).**

Figure 1 Study design.



Inclusion Criteria:

1. Liver cirrhosis confirmed clinically, in the laboratory, or through radiology by ultrasonography (classical finding of cirrhosis) -(Child–Pugh A or B).
2. Patients with esophageal or fundal varices.
3. No previous history of gastrointestinal bleeding.

Exclusion Criteria:

1. Age < 16 and > 75 years.
2. History of recurrent bleeding varices and band ligation or injection sclerotherapy.
3. Portal vein thrombosis.
4. Hepatocellular carcinoma.
5. Patients with Child–Pugh score C.
6. Comorbid renal failure, COPD, or bronchial asthma.
7. Renal impairment
8. Contraindications or allergy to atorvastatin.
9. Contraindications to beta-blockers (COPD, aortic stenosis, bronchial asthma).

Sample size: The sample size was estimated using Epi-info software created by WHO and CDC, version 2002. We considered 95% confidence limit. -80% power of the study. -expected outcome (portal venous pressure reduction) in the treatment group 90% compared to 50% for control group.

The total sample size based on the above criteria was calculated 40 ,at N ≥20 for each study group.

Methods:

All patients subjected to :

- Full history, clinical examinations, and laboratory investigations and abdominal ultrasonography.
- Also, Doppler ultrasound and upper endoscopy for both groups before and after two months of starting treatment.

Doppler Ultrasound

Doppler ultrasound assessments were performed in the diagnostic radiology department with a Philips (EPIQ 7) using a 3.5 MHz convex probe. Evaluation was done in the supine position after 6 hours fasting using both B mode and Doppler ultrasound. Patients were asked to hold breath for appropriate Doppler assessment.

All parameters were measured by a radiology specialist. The probe was placed in the porta hepatis and at the splenic hilum. We tried to unify the method for measurement to avoid interobserver variability. Portal vein diameter (PVD) was measured in millimeters **(Fig.2).** The peak, smallest, and mean flow velocity was recorded in CC/min then portal vein flow volume (PVFV) was automatically calculated.

Figure 2 **a.** Gray scale ultrasound image showing measurement of caliber of dilated portal vein at porta hepatis. **b.** Color scale ultrasound image showing full color saturation of portal vein with measurement of portal vein flow volume=730cc/min. **c.** Color scale US image showing full color saturation of hepatic artery with RI=0.74, PI=1.5, PSV=111 cm/s.

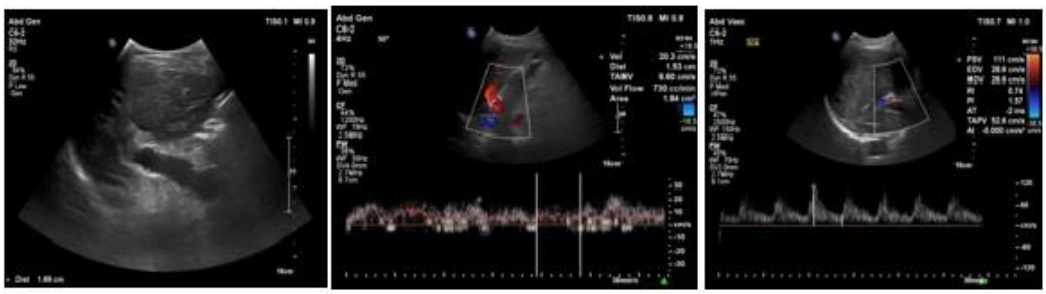


Fig 2a fig2b fig2c

Hepatic artery resistance index (HARI) was calculated using the following formula: [peak systolic velocity (V max) – end diastolic velocity/peak systolic velocity (V min)/mean velocity].

We also assess the direction of flow in portal vein, portal vein velocity (PVV) in (cm/sec). hepatic artery pulsatility index, and splenic artery resistance index (SARI).

Upper endoscopy:

Before and after patients received treatment, upper endoscopy was carried out by a single endoscopist using a **Pentax EG-3490 k type gastroscope** at the same endoscopy unit after overnight fasting and conscious sedation. Grading of the size of esophageal varices was done by the Paquet grading system **[20]**

The presence of fundal varices, portal hypertensive gastropathy were also evaluated.

Statistical analysis

We used Statistical Package for Social Sciences (SPSS) version 21. The qualitative variables were presented as number and percent, We used Chi-square test for analysis. We used independent samples and paired t- test for comparison of means values between groups. Sign test was used for analysis of paired ordinal categorical variables. P value (≤ 0.05) was considered significant.

RESULTS:

Our study enrolled 40 patients with Child–Pugh A cirrhosis were enrolled from September 2019 to September 2020. The patients in the study were randomized to either receive 40 mg of propranolol and 20 mg of atorvastatin daily or 40 mg of propranolol alone daily for 2 months. Our study showed no differences between the both groups regarding age, sex, and laboratory investigation **(Table 1)**.

Doppler study of the groups showed:

There was a statistically significant difference in PVD before and after two months of atorvastatin and propranolol (P-value = .039); also, there were highly statistically significant differences in both groups (A and B) in PVV and PVFV. There was a statistically significant difference in each group in HARI and HAPI before and after receiving the treatment. No significant difference was found in SPARI in both groups **(A and B)**.

The detailed baseline and hemodynamic parameters of patients who received atorvastatin and 40 mg of propranolol and propranolol alone are shown in **Table 2.**

Endoscopic comparison of the studied groups showed:

There was a highly statistically significant difference in endoscopic grading (variceal size) before and after two months of 40 mg of propranolol and 20 mg of atorvastatin (P-value = .000). However, there was no statistically significant difference in endoscopic grading in patients who received 40 mg of propranolol alone (P-value = .687; Table 3).

Table (1): Baseline Clinical and Hemodynamic Characteristics of Patients.

	Statin and propranolol	propranolol	P value
Age (year)	51.50 ± 7.21	49.75 ± 7.86	.468
Sex **Male**, n (%) **Female**, n (%)	 11 (55) 9 (45)	 12 (60) 8 (40)	 .602
Laboratory Investigation			
Hb (g/dl)	14.22 ± 1.27	14.34 ± 1.13	.755
WBCs (g/dl)	6.02 ± 1.81	5.86 ± 2.47	.817
RBCs (g/dl)	4.86 ± .45	4.92 ± .29	.607
MCV (g/dl)	88.25 ± 6.52	88.55 ± 4.52	.867
PLT (g/dl)	131.20 ± 21.38	161.80 ± 73.00	.08
Liver function tests:			
Total BIL(mg/dl)	18.37 ± 7.95	13.58 ± 11.35	.130
Direct BIL(mg/dl)	9.87 ± 5.57	6.27 ± 4.76	.034*
Total Protein	72.54 ± 8.15	78.74 ± 5.58	.008*
Albumin	26.36 ± 17.50	33.02 ± 12.81	.178
SGPT	70.88 ± 27.43	67.00 ± 34.94	.698
SGOT	72.98 ± 25.30	56.47 ± 20.52	.029*
GGT	157.40 ± 160.64	118.22 ± 69.66	.323
ALP	108.60 ± 43.18	98.45 ± 43.71	.465
Prothrombin time	13.87 ± 2.34	12.88 ± 1.06	.095
Prothrombin conc.	77.52 ± 17.96	81.82 ± 15.66	.425
INR	1.18 ± .19	1.09 ± .09	.053
Renal function tests:			
Urea (mmol/l)	7.28 ± 5.67	4.87 ± .94	.069
Creatinine (mmol/l)	98.63 ± 26.91	87.99 ± 12.08	.115

***significant**

Data expressed as range and mean± SD. PT: prothrombin time, PC: prothrombin concentration, INR: international normalized ratio, ALP: alkaline phosphatase, WBCs: white blood cells, RBCs: red blood cells, Hb: hemoglobin, MCV: mean corpuscular volume.

Table (2): Doppler parameters of the studied groups.

	Statin and propranolol	propranolol	T	P value
PVD				
Baseline	13.47 ± 2.36	14.35 ± 1.95	1.288	.206
2 months after	13.86 ± 2.13	14.46 ± 1.87	.942	.352
P value	.039*	.414		
PVV				
Baseline	10.42 ± 1.62	12.42 ± .56	5.178	.000*
2 months after	12.08 ± 1.21	13.35 ± .66	4.135	.000*
P value	.000*	.000*		
PVFV				
Baseline	647.59 ± 177.23	882.70 ± 174.73	4.225	.000*
2 months after	739.66 ± 128.07	920.51 ± 158.71	3.966	.000*
P value	.000*	.001*		
HARI				
Baseline	.75 ± .07	.72 ± .06	1.407	.167
2 months after	.70 ± .05	.69 ± .04	.655	.516
P value	.000*	.000*		
HAPI				
Baseline	1.67 ± .29	1.55 ± .24	1.468	.150
2 months after	1.51 ± .16	1.45 ± .18	1.173	.248
P value	.000*	.000*		
SPARI				
Baseline	.71 ± .05	.71 ± .06	.413	.682
2 months after	.67 ± .11	.69 ± .038	.906	.370
P value	.126	.175		

***significant**

PVD: Portal vein diameter, PVV: Portal vein velocity, PVFV, HARI: Hepatic artery resistance index, HAPI: Hepatic artery pulsatility index

Modified liver vascular index, SPARI: Splenic artery

Table (3): Endoscopic comparison of the studied groups.

	No varices n (%)	OV GI n (%)	OV GI, fundal extension n (%)	OV GII n (%)	OV GII, fundal extension n (%)	OV GIII, n (%)	P value
Group A							
Endoscopic before:	0 (0%)	2 (10%)	2 (10%)	8 (40%)	2 (10%)	6 (30%)	**.000***
Endoscopic after:	5 (25%)	9 (45%)	2 (10%)	4 (20%)	0 (0%)	0 (0%)	
Group B							
Endoscopic before:	0 (0%)	8 (40%)	3 (15%)	6 (30%)	0 (0%)	3 (15%)	**.687**
Endoscopic after:	0 (0%)	6 (30%)	3 (15%)	11 (55%)	0 (0%)	0 (0%)	

***significant**

OV: esophageal varices.

DISCUSSION

Dietary components, especially the type and the Portal hypertension, considered to be a serious complication of liver cirrhosis, with increase in the flow resistance inside the portal vein, leading to the formation of GOVs (***16***). This study was a randomized controlled clinical trial to evaluate the effect of adding statins to

decrease portal pressure; Doppler ultrasound and upper endoscopy were performed on cirrhosis patients prior to and after starting one group on 20 mg of atorvastatin and 40 mg of propranolol and another control group on 40 mg of propranolol alone.

Our study showed no significant difference in the age or laboratory study between the both studied groups, However Doppler study and upper endoscopic findings before and after the start of treatment showed significant difference between the two groups.

This study showed that there is a statistically significant difference in PVD before and after two months of statin and propranolol (P-value = .039). A similar finding was in a study by **Nadia et al**. who concluded that statin could lower the intrahepatic resistance and PHT **[17].**

Our result showed that the mean PVV and mean PVFV were less than 16 cm/sec in both groups. This was similar to the findings of **Lafortune and colleagues [21]** who claimed that decrease the velocity <16 cm/sec is a major sign of PHT in cirrhotic patients that may be related to the increase in portal resistance and pressure. Two another studies were in line with ours and concluded that PVV decrease in patients with PHT **[22, 23].**

Our study showed that there were increase in the baseline HARI and HAPI in both groups. Increase in the intrahepatic arterial resistance with portal hypertension may be the cause. This was in line with Yu Ya study that revealed that HARI increase in patients with portal hypertension than those without [24].

Furthermore, there was a statistically significant difference in each group in HARI and HAPI before and after receiving the treatment, and the decrease in HARI and HAPI was greater in group A. Treatment induced hepatic satellite cell modification and lowering the portal pressure may be the cause of this decrease in the hepatic resistance. ***Abraldes et al.*** found that statin exert intrahepatic vasodilatation through upregulation of NO production **[10].**

An interesting finding of our study that there was no statistically significant difference between both groups (A and B) in terms of SPARI. ***This in agreement with Zhang et al. observed*** that SPARI not significantly affected by change in the portal pressure. [**25].**

Our study showed that there was a statistically significant difference in endoscopic grading (variceal size) before and after two months of 40 mg of propranolol and 20 mg of atorvastatin. However, there was no statically significant difference in endoscopic grading in patients who received 40 mg of propranolol alone**.** This was in line with *Vargas* et al. [26] that reported that statins could decrease the portal pressure and control the portal hypertension.

Our study limitation include: relatively small size and short period of follow up we did not include cirrhotic patients child C.

CONCLUSION

In conclusion, atorvastatin significantly decreased the intrahepatic resistance and PHT in cirrhotic patients. Statin significantly enhance liver blood flow, as demonstrated by the increased modified liver vascular index in patients with cirrhosis and PHT. So, statin could be a safe therapy for PHT in patient with Child A and B.

Abbreviations:

PHT: portal hypertension, PVD: portal vein diameter, PVV: portal vein velocity, PVFV: portal vein flow volume, HARI: hepatic artery resistance index, HAPI: hepatic artery pulsatility index, and SARI: splenic artery resistance index

Conflict of Interest: None.

Funding: None.

Ethical considerations: This study was approved by Kafrelsheikh university ethical committee and followed the Declaration of Helsinki. Written consent was obtained after explanation of the research.

HIGHLIGHTS

- ✓ For lowering portal hypertension, atorvastatin and propranolol are more effective than propranolol alone.
- ✓ Statin could be a valuable therapy for PHT.
- ✓ Statin significantly improved liver perfusion, as demonstrated by the increased modified liver vascular index in patients with cirrhosis**.**

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