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Evaluation of the Difference between Cirrhotic Patients Receiving Propranolol and Those Receiving Propranolol Plus Losartan in terms of Renal Artery Resistive Index

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ABSTRACT

Introduction:
Portal hypertension is one of the main clinical complications of chronic liver diseases. In only 30% of cirrhotic patients who take propranolol, the hepatic venous pressure reduces to under 12 mm/Hg. The results of studies on the efficiency of losartan (an angiotensin II receptor antagonist) in reducing portal hypertension have been controversial so far. Hepatic venous pressure gradient (HVPG) is measured using an invasive method of catheterization. Studies have shown that the measurement of the renal resistive index (RI) by Doppler ultrasonography has a direct relationship with HVPG. The study population included cirrhotic patients who referred to Ali-ibn-Abi Talbe Clinic, Zahedan, Iran. This clinical trial was conducted based on a self-controlled method.

Materials and Methods:
In total, 30 cirrhotic patients who met the inclusion criteria were selected for the study. The patients were treated with propranolol 10 mg twice a day for one month, and losartan was then added to their medication regimen. The renal RI of patients was measured before and after losartan administration.

Results:
The mean of renal RI of patients treated with both propranolol and losartan (0.659±0.58) was higher than that of the patients treated with only propranolol (0.635±0.597) (P=0.005).

Conclusion:
Our results showed that cirrhotic patients who received propranolol had high renal RI before and after receiving losartan. Accordingly, it seems that losartan had no effects on reducing HVPG hypertension in patients taking propranolol.

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Introduction

Portal hypertension is one of the main clinical complications of chronic liver diseases. Ascites, hepatic encephalopathy and variceal bleeding are major causes of death and liver transplant in these patients. There is a positive association between high hepatic venous pressure gradient (HVPG) and propranolol-induced HVPG reduction indicating that pharmacological treatment also benefits patients with advanced portal hypertension (1). Pharmaceutical treatment aims to reduce hepatic venues pressure to more than 20% of its baseline or below 12 mmHg (2-4), which decreases the risk of bleeding and increases patient survival (5). This target is achieved only in 30% of patients treated with propranolol (6,7). On the other hand, there is no dose-dependent effect of propranolol on the treatment of portal hypertension (8). The propranolol's adverse effects and its low efficacy have stimulated the search for alternative medications for portal hypertension (2, 4). The effects of angiotensin receptor blockers have been studied since two decades ago (9, 10). Since losartan reduces HVPG noticeably in cirrhotic patients without any side effects (11), it can be an appropriate agent to add to propranolol. However, there are controversies in the results of studies investigating the losartan efficacy in reducing portal hypertension and inducing arterial hypotension (as its side effect) (4, 11). Accordingly, the potential use of losartan in the treatment of portal hypertension is still under debate (2). Different studies compared the effects of losartan (25 mg daily) with propranolol (30 mg daily) on reducing portal pressure in cirrhotic patients. In these studies, the portal pressure was measured at baseline and after the treatment period using an invasive method of fluoroscopy (inserting a 5f balloon catheter through the basilica vein) (2-4,12,13). Some studies used Doppler ultrasonography as a non-invasive method to measure HVPG and found no relationship of HVPG with portal vein Doppler and response to treatment (13,14). In this regard, some studies showed that an increase in the renal RI is associated with hepatocellular diseases and portal hypertension; moreover, they concluded that Doppler ultrasonography of the kidney might be used as a non-invasive method for determining HVPG (15,16). Therefore, Doppler ultrasonography of the kidney is a simple and cheap way to identify portal hypertension at follow-up in cirrhotic patients (11).

In resource-constraint areas where portal hypertension measurement facilities are unavailable, Ultrasound could be useful in monitoring response and compliance to beta-blockers (17). Most of the studies showed conflicting results about the losartan effect on portal hypertension (2-4,11). In one study, losartan reduced portal hypertension by 20% (11), and an equal number of responders reported that the reduction of HVPG was greater in the losartan group, compared to the propranolol group (18). In a study, losartan was effective only in severe portal hypertension (2), and in another one, losartan had a similar effect as propranolol (3,19).

According to the results of one study, angiotensin receptor blockers (ARBs) did not reduce portal pressure in patients with cirrhosis; moreover, the risk of symptomatic hypotension might increase (20). Kim JH et al. showed that the addition of one kind of ARB (e.g., candesartan) to propranolol conferred no benefit relative to classical propranolol monotherapy for the treatment of portal hypertension, and therefore, it was not recommended (21).

The above studies have not been controlled properly or may have biases. Since the direct measurement of HVPG is invasive and renal RI, as well as HVPG, are related, this study was conducted on 30 cirrhotic patients with self-control. In addition, this study aimed to evaluate the difference between cirrhotic patients who were treated with propranolol and those treated with propranolol plus losartan in terms of renal RI. It should be mentioned that the patients were selected from Ali-ibn-Abi Taleb clinic, Zahedan, Iran.

Materials and Methods

This clinical trial was conducted based on a before-after design. The study population was cirrhotic patients who were residents in Zahedan, Iran, the cirrhosis of whom was confirmed by hepatic biopsy, clinical symptoms, and ultrasonography.

Sample size and sampling method

Most of the previous study had compared the effects of propranolol alone with Most of the previous studies compared the effects of propranolol alone with losartan on the HVPG, whereas the results of propranolol treatment with propranolol plus losartan treatment on HVPG were compared in this study. Since information about losartan and propranolol effectiveness in reducing HVPG is contradictory, and their effects on renal RI in cirrhotic patients are not well known, the Gehan table could not be utilized to estimate the sample size. Accordingly, considering the central limit theorem, 30 patients were selected for this study. This study is a before-after clinical trial since cirrhotic patients who were similar to the case group regarding Child-Pugh Score, esophageal varices, and ascites could hardly be found. As a result, the most similar person to a patient is the patient himself.

The inclusion criteria were 1) age of 18 to 75 years old, 2) blood pressure more than 100 mm hg, 3) oesophageal varices with a degree more than two diagnosed by endoscopy, 4) at least one-month history of using propranolol (10 mg) twice a day, and 5) confirmed cirrhosis based on biopsy, clinical symptoms, ultrasonography, or analytical findings. On the other hand, the cirrhotic patients with Child-Pugh Score who had heart failure; alcoholic patients; and those with liver cancer, kidney failure, serum creatinine over 2mg/cc, any contraindication for using propranolol or losartan, and history of variceal bleeding in the last four weeks were excluded from the study. The patients were fully informed about the study procedure, and written consent was obtained from them. Following that, the cirrhotic patients who used propranolol (10 mg) twice a day during the last month were introduced for ultrasonography after one-night fasting. They were then situated in the supine position and Doppler ultrasonography GE logiq7 with 3.5 probe or five MHz was used to evaluate them. Doppler signals were obtained from interlobar arteries along the border of medullary pyramids or arcuate arteries at the corticomedullary junction. The Doppler waveforms were made on the lowest frequency-shift range possible without aliasing with a wall filter of 100.

The RI for each kidney was calculated as an average value obtained from three waveforms recorded in three different regions of the kidney. Afterward, a mean renal RI was calculated for each patient (average of both kidneys). Based on the results of other studies, there was no difference between right and left renal RI. However, both sides of the RI were calculated using the above method, and their mean scores were obtained. An RI of 0.70 or more was considered abnormal, which indicated elevated renal vascular resistance and renal vasoconstriction.

Subsequently, the patients were treated with propranolol (10 mg) twice a day plus losartan (12/5mg) twice a day at 8 a.m. and 8 p.m. for two weeks. Furthermore, they were advised to rest for 3-4 hours after taking the first dose of losartan. After two weeks of treatment, the patients' renal RIs were evaluated by Doppler ultrasonography using the same method as the first time. The patients' blood pressure was controlled three days after commencing losartan and at the end of two weeks. In addition, their serum creatinine, K, and urea have been checked at the beginning of treatment with losartan as well as the last day.

Data analysis

The collected data were analyzed in SPSS software (version 11; SPSS inc. Chicago, ll, USA) through the paired t-test. The renal RI of patients before and after taking losartan was compared in this study. A p-value less than 0.005 was considered statistically as significant.

Ethical considerations

The study protocol was fully explained to the patients, and informed consent was obtained from them before participating in the study.

Ethical issues

This study was extracted from a medical residency dissertation by Ladan Fakhryehasl, MD, (NO.72599/Proposal NO.1745) submitted to the Zahedan University of Medical Sciences, Zahedan, Iran.

Data analysis

The data were analyzed in SPSS software (version 15), and they were expressed as mean+standard deviation (SD). The paired student t-test was utilized for comparison baseline within each group; in addition, the between-group comparisons were performed using the unpaired student t-test. Furthermore, Fisher's exact test was employed for percentage comparisons. A p-value less than 0.05 was considered statistically significant.

Results

In total, 32 cirrhotic patients who met the inclusion criteria were recruited for the study, and two patients were excluded due to unwillingness to cooperate during the study period. The majority of the cases were male (n=19; 63.7%) with a mean age of 42.5±14 years. The causes of cirrhosis were hepatitis B (60%) and idiopathic (40%). Furthermore, 63.7% and 36.7% of the patients were in Child-Pugh class A and B, respectively. Regarding the duration of the disease, the longest and shortest duration lengths were 6 and 1 years (mean duration: 2.8 years). According to the results of the paired t-test, the mean±SD of renal RI in patients treated with propranolol alone was obtained at 0.635±0.0597. On the other hand, the mean±SD of renal RI in patients treated with propranolol plus losartan calculated by paired t-test was determined at 0.659±0.058. Considering P=0.005, an increase in the renal RI in patients after losartan administration was statistically significant (Diagram1 and Table 2).

Table 1: Baseline characteristics of the study population

Baseline characteristics	Number% (Mean±SD)
Gender	
Male	63.3%
Female	36.7%
Age	42.5±14
Severity of Cirrhosis	
Child-Pugh Class A	63.3%
Child-Pugh Class B	36.7%
Etiology	
HBV	60%
HCV	-
Alcohol	-
Autoimmune hepatitis	-
Idiopathic	40%

Table 2: Comparison of cirrhotic patients taking propranolol and propranolol plus losartan in terms of renal RI

	Mean	SD	P-value
Renal RI of cirrhotic patients taking propranolol only	0.635	0.597	0.005
Renal RI of cirrhotic patients taking propranolol plus losartan	0.659	0.580	0.005

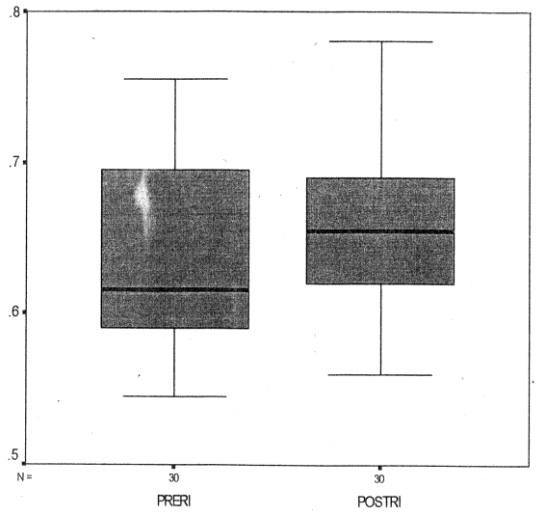

Fig 1: Change in the mean of renal RI of cirrhotic patients under propranolol after taking losartan

Discussion

A large amount of evidence supports the hypothesis that angiotensin II plays a role in the physiopathology of portal hypertension (2-4,11). According to these studies on cirrhosis, angiotensin II contributes to the variable component of intrahepatic resistance in portal hypertension. This has provided a rationale for several trials examining the effects of angiotensin-converting enzyme inhibitors and ARBs (22-25). The key pharmacological molecules are the classical renin-angiotensin system (RAS) pathway antagonists and alternative pathway agonists that may offer strategies for the treatment and prevention of chronic liver disease and portal hypertension (26). The RAS is usually activated in patients with advanced cirrhosis, and a direct relationship has been observed between plasma renin activity and HVPG (2). The activation of RAS worsens portal hypertension, which itself causes hepatic fibrosis, and consequently, deteriorates cirrhosis.

Schneider et al. studied two case groups with HVPG >20 mmHg (n=30) and HVPG <20 mmHg (n=15) who were treated with losartan (25 mg) daily for a week in Germany during 1999. On the other hand, the control group included 15 cirrhotic patients with HVPG>20 mmHg and 10 patients with HVPG<20 mmHg, none of them took losartan. The result of their comparison showed that in all the patients with high HVPG, except for one of the patients with moderate HVPG, losartan caused a 20% reduction in HVPG pressure (9).

In the same line, Gonzalez-Abraldes et al. conducted a controlled trial in Spain during 2001. They administrated losartan to 25 cirrhotic patients and propranolol to 15 cirrhotic patients for six weeks. The results showed that losartan was not a good substitute for propranolol in preventing variceal bleeding (3).

Similarly, Castano et al. performed a clinical trial in Mexico during 2003. They randomly assigned 27 patients into two groups who were treated with losartan (25 mg) daily (n=17) and propranolol (n=10). Their results showed that propranolol decreased the HVPG significantly (P=0.07), and losartan (25 mg) daily might be effective in the reduction of portal hypertension in patients with compensated cirrhosis, especially those with high portal hypertension (1).

Debk et al. investigated the effects of losartan and propranolol on portal hypertension in India during 2003. They administrated losartan and propranolol to two groups of patients for two weeks. The HVPG was measured on the first day and the 14th day. The results revealed that losartan was more effective than propranolol for decreasing portal hypertension and preventing variceal bleeding in cirrhotic patients without ascites and with alcoholic cirrhosis (2). In the same vein, Berzigottie et al. in 2006 and Coli et al. in 2001 investigated the direct relationship between the renal RI of cirrhotic patients and HVPG in patients with varices and demonstrated that portal pressure increased in patients after losartan administration (11).

Hiujing Yao et al. conducted a randomized control trial on 394 patients in 2018 and revealed that treatment with ARBs did not significantly change HVPG, compared to controls. These results were consistent with the findings of the studies comparing ARBs with propranolol (27). However, Jianrong Wang et al. in 2017 showed that the β-blocker combination therapy and renin-angiotensin-aldosterone system inhibitor reduced portal hypertension significantly and to a greater extent, compared to β-blocker monotherapy (28). Previous studies illustrated controversial results regarding losartan effectiveness in reducing portal hypertension (2-4,11).

Our study is a combination of few studies for comparing renal RI in cirrhotic patients treated with propranolol and those treated with propranolol plus losartan. However, it has few differences from previous studies. First, to our knowledge, no other studies evaluating the losartan indirect effect on HVPG by measuring renal RI.

Furthermore, the causes of cirrhosis were hepatitis B and idiopathic in our study subjects, and there was no patient with alcoholic cirrhosis that could be an explanation for the inefficacy of losartan in our samples. Previous studies that showed an 81% response rate to losartan, compared to 27.2% response to propranolol (P< 0.05), have been conducted on patients with alcoholic cirrhosis. In patients with alcoholic cirrhosis, a complex activity of stellate cells, an increase in perisinusoidal collagen, and an increase in hepatocyte size, cause sinusoidal portal hypertension; therefore, losartan reduces their portal hypertension significantly.

Conclusion

Our study results showed that based on comparing renal RI of cirrhotic patients treated with propranolol and those treated with propranolol plus losartan, the renal RI of patients increased significantly after losartan administration (P=0.005).

It is concluded that losartan is not an appropriate medication for decreasing HVPG in cirrhotic patients who receive propranolol. It is recommended to perform larger studies with a larger sample size to evaluate this theory.

One of the limitations of our research is that renal US is not a gold standard for portal HTN.

Ethical considration

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. Informed consent was obtained from the patients.

Acknowledgment

This study was extracted from a medical residency dissertation by Ladan Fakhryehasl, MD, (NO. 72599/ Proposal NO.1745) submitted to the Zahedan University of Medical Sciences, Zahedan, Iran.

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