Carvedilol Versus Propranolol in the Prevention of Variceal Rebleeding in Hepatic Schistosomiasis: Efficacy and Safety

Chantelli Iamblaudiot Razafindrazoto (iamblaudiotchantelli@yahoo.com)
University Hospital Joseph Raseta Befelatanana

Lova Dany Ella Razafindrabe Koto
University Hospital Andrainjato

Domoina Harivony Hasina Laingonirina
University Hospital Joseph Raseta Befelatanana

Raveloson Raveloson
University of Fianarantsoa

Anjaramalala Sitraka Rasolonjatovo
University Hospital Joseph Raseta Befelatanana

Andry Lalaina Rinâ Rakotozafindrabe
University Hospital Joseph Raseta Befelatanana

Tovo Harimanana Rabenjanahary
University Hospital Joseph Raseta Befelatanana

Soloniaina Hélio Razafimahefa
University Hospital Andrainjato

Rado Manitrala Ramanampamonjy
University Hospital Joseph Raseta Befelatanana

Research Article

Keywords: Schistosomiasis, propranolol, carvedilol, Madagascar

DOI: https://doi.org/10.21203/rs.3.rs-625472/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

**Background:** The betablockers combined with endoscopic variceal band ligation (EVL) is the most effective prevention of variceal rebleeding. The aim of this study is to evaluate the efficacy and safety of carvedilol compared to propranolol as secondary prevention of variceal bleeding in hepatic schistosomiasis.

**Methods:** All patients with portal hypertension due to schistosomiasis presenting for EVL with at least one episode of variceal bleeding were included and randomized into propranolol + EVL and Carvedilol + EVL groups.

**Results:** Sixty-one patients were selected and randomized into the propranolol group (n=30) and carvedilol group (n=31). We noted less recurrence of bleeding in the carvedilol group (n=1) than in the propranolol group (n=3) (3.33% vs 10%; p=0.30). Bleeding recurrence occurred after 30 days in the carvedilol group and after 5, 45 and 90 days in the propranolol group. At 4 months, a significant reduction in mean arterial pressure (-4.13 mmHg; 95%CI: -6.27 and -1.99; p <0.05) and heart rate (-12.13 mmHg; 95%CI: -13.92 and -10.35; p<0.05) was found in the carvedilol group. There was no significant difference between the two groups on the mean difference in mean arterial pressure. A patient in the carvedilol group presented breathing difficulty. No adverse effects have been demonstrated in the propranolol group.

**Conclusion:** Carvedilol is as effective as propranolol in the prevention of variceal rebleeding in hepatic schistosomiasis.

Introduction

Schistosomiasis is a parasitic disease caused by trematodes of the genus Schistosoma (S.). It is the third major parasitic endemic worldwide after malaria and amebiasis [1, 2]. It is a public health burden in developing countries. In Africa, schistosomiasis remains the most common cause of portal hypertension, far ahead of viral hepatitis-induced cirrhosis or alcoholic cirrhosis [3, 4]. In addition, esophageal varices bleeding is a major cause of morbidity in patients with non-cirrhotic portal hypertension in developing countries [3]. In Madagascar, intestinal schistosomiasis is a real burden in certain regions including the Haute Matsiatra region, located in the south of Antananarivo [5]. The utility of non-selective betablockers (NSBB) in the primary and secondary prevention of variceal bleeding in cirrhotic patients is well established [6]. Unlike cirrhosis, published data on the effect of betablockers on post-schistosomiasis portal hypertension is scarce and controversial. Propranolol was the first widely studied molecule in the prevention of esophageal varices bleeding during cirrhotic and non-cirrhotic portal hypertension (hepatic schistosomiasis). Carvedilol is an alternative to propranolol [6]. Moreover, it is recommended, along with propranolol during the primary prevention of variceal bleeding [7]. In fact, more than half of patients do no response to propranolol [8]. Carvedilol decreases portal pressure more compared to propranolol [8]. To our knowledge, no data is available on the efficacy and safety of carvedilol in the prevention of variceal...
rebleeding in hepatic schistosomiasis. The aim of this study was to evaluate the efficacy and safety of carvedilol compared to propranolol as secondary prevention of variceal bleeding in hepatic schistosomiasis.

Materials And Methods

Study population

This was a prospective, comparative, randomized study, within the department of Internal Medicine, University Hospital Tambohobe and department of Gastroenterology - Internal Medicine, University Hospital Andrainjato, Fianarantsoa over a period of 14 months, from February 1, 2019 to March 31, 2020. All patients with portal hypertension due to schistosomiasis and history of variceal bleeding were recruited. All patients presenting for endoscopic variceal band ligation (EVL) with at least one episode of variceal bleeding were included. All patients with the presence of a contraindications to betablockers (Asthma, COPD, AVB, HR ≤ 40 bpm, etc.) and refusal to participate in the study were excluded. The hepatic schistosomiasis diagnostic criteria were the presence of clinical signs (ascites, collateral venous circulation, splenomegaly), ultrasound signs (visualization of portosystemic collaterals, enlarged portal vein ≥ 15mm, splenic vein dilation ≥ 10mm and splenomegaly) and endoscopic signs (esophageal varices and portal hypertension gastropathies) and positive schistosomiasis serology. The variables studied were demographic data (age, gender), clinical data (ascites, splenomegaly, number of previous bleeding episodes), laboratory data (platelet count, serum creatinine, albuminemia, bilirubin, ALT, Prothrombin activity, markers of viral hepatitis), ultrasound data (portal vein diameter, periportal fibrosis), endoscopic data (size of the esophageal varices, presence of red signs), hemodynamic response (SBP, DBP, MAP, HR), hemorrhagic recurrence, decompensation occurrence, side effects (low blood pressure, postural hypotension, bradycardia, cold extremities, chest pain, headache, dizziness, asthenia, impotence, digestive disturbances, skin lesions, central nervous system disorders) and death occurrence.

Methodology

The patients will be split alternately two groups: carvedilol group and propranolol group. The randomization of the patients was done alternately. The initial dose of carvedilol was 6.25 mg once a day, up to a maximum dose of 25 mg daily. Propranolol was started at a dose of 20 mg daily and gradually increased to a dose of 80mg or 160 mg daily. The doses of betablockers were increased every 3 to 5 days. Patients who were already on propranolol, retained the usual pre-EVL dose. The intake or resumption of betablocker treatment was started the day after the EVL. Regular patient monitoring was carried out: at the time of inclusion, at the time of each EVL session (hospitalization) and 15 days after each EVL session (outpatient consultation), until the 4th month. The EVL sessions were done monthly, until the esophageal varices were eradicated. The patient was free to leave the study at any time. In case of rebleeding, the patient was hospitalized and supportive cared according to a standardized protocol. If a side effect, the betablocker treatment was substituted for the one that was not been used.

Endpoints and outcomes
The effectiveness of the betablocker used was judged on the absence of rebleeding over a 4 months period. Safety assessment was judged on the presence of side effects and the hemodynamic response.

**Statistical analysis**

Statistical analyses were performed using SPSS Statistics (version 22.0; IBM, Chicago, IL, USA). Continuous variables were expressed as means ± standard deviations or median and range. Descriptive characteristics were as numbers (percentages) for the categorical variables. Differences between groups were analyzed using the Chi-square test for categorical variables and Student’s *t* test or Mann-Whitney *U* test for continuous variables as appropriate. A two-tailed *p* value <0.05 was considered statistically significant.

**Results**

During the study period, a total of 63 patients experienced at least one variceal bleeding episode from which two patients were excluded. The remaining 61 patients were randomized to the carvedilol group (n = 31) and the propranolol group (n = 30). There was no significant difference in demographic variables and baseline patient characteristics between the two groups (Table 1).

**Treatment outcomes**

Lower rebleeding was observed in the carvedilol group compared to propranolol group (3.33% versus 10%), but without significant difference (Table 2). Bleeding recurrence occurred after 30 days in the carvedilol group and after 5, 45 and 90 days in the propranolol group. We noted two eradictions of esophageal varices in the carvedilol group and none in the propranolol group. No deaths were found in the two groups.

**Effect on hemodynamic parameters**

The median dose of propranolol to achieve a heart rate between 55–60/min was 60mg/day (20-80mg/day) and that of carvedilol 12.5mg/day (6.25-25mg) (Table 1).

There was no significant difference in initial heart rate (HR), systolic (SBP), diastolic (DBP), mean (MAP) arterial pressure between the two groups (Table 3). At 4 months of treatment, our results showed a significant reduction in hemodynamic parameters in the carvedilol group (Table 4). This reduction was not significant between the two groups (Propranolol vs. Carvedilol) apart from HR (-8.03 vs -12.13; *p* = 0.005). The results were calculated as a percentage change. We objected to a significantly higher mean percentage change in HR in the carvedilol group than in propranolol (16.08±5.29 vs 10.94±7.64; *p* = 0.003).

**Tolerance and adverse effects**
There was no significant difference between the two groups in terms of side effects. One patient in the carvedilol group experienced a severe side effect such as breathing difficulty and had to withdraw from the study. No patient in the propranolol group had any adverse effects (Table 2).

**Discussion**

Based on existing literature data, it appears that carvedilol has more potent desired physiological effects compared to propranolol. The BAVENO VI Consensus recommends carvedilol along with propranolol and EVL for the primary prophylaxis of variceal bleeding [7]. A few trials comparing carvedilol with EVL for primary prevention showed promising results in favor of carvedilol [6, 9, 10]. According to Reiberger [11], in cirrhotic patients, as primary prevention, carvedilol caused a reduction in hepatic vein pressure gradient (HVPG) in patients not responding to propranolol, thus leading to fewer bleeding episodes with a lower rate of bleeding over 2 years of 5% (vs. 11% with propranolol and 25% with EVL; $p = 0.0429$). The combination of betablockers and EVL is the recommended of prevention of variceal rebleeding in patients with cirrhotic or non-cirrhotic portal hypertension [7].

To our knowledge, this present study is the first to directly evaluate carvedilol compared to propranolol as secondary prevention of variceal bleeding in hepatic schistosomiasis. Despite its limitations, this study demonstrates a reduction in the incidence of variceal rebleeding in carvedilol group compared to propranolol group (3.33% vs 10%, $p = 0.3009$). Numerous series had demonstrated the efficacy of propranolol in secondary prevention during non-cirrhotic portal hypertension, in terms of reducing the incidence of hemorrhagic recurrence. Kiire et al in 1989 [12] showed that propranolol reduced the rate of hemorrhagic recurrence in patients with non-cirrhotic portal fibrosis compared to placebo group (5/25 vs. 20/25; $p<0.001$). Tourabi et al in 2016 [3], confirmed the results of Kiire et al (1/42 vs 8/40; $p<0.02$). There is little data on carvedilol for prevention of variceal rebleeding and these data were studied in cirrhotics. The evidence for carvedilol in the prevention of variceal rebleeding is minimal but promising. Lo et al in 2012 [13], had objected that carvedilol is as effective in terms of reduction of bleeding recurrence as the combination nadolol and isosorbide mononitrate (51% vs 43%; $p = 0.46$). Gupta et al [14], in a cirrhotic population, found a similar proportion of rebleeding between carvedilol and propranolol (1/30 vs 1/29; $p = 0.74$). An interim analysis of a multi-center randomized controlled study comparing carvedilol to EVL showed no significant difference in terms of bleeding recurrence (37.5% vs 29%; $p = 0.72$) [15]. A meta-analysis including 13 studies with 1598 patients demonstrated the superiority of carvedilol to EVL in the prevention of variceal rebleeding [16]. A meta-analysis according to Yang et al [17], including 802 patients (402 carvedilol patients and 400 propranolol patients) showed that carvedilol was more effective than traditional NSBB with a decrease in the rate of variceal rebleeding (OR: 0.53; 95% CI: 0.38–0.75; $p = 0.0003$). The result of this study seems to suggest carvedilol as an alternative in the prevention of variceal rebleeding. Although the results of this study are promising in favor of carvedilol, a large and long-term study would be needed to substantiate and confirm this benefit in terms of variceal rebleeding in hepatic schistosomiasis.
In terms of hemodynamic effect, carvedilol at a median dose of 12.5 mg/day (6.25-25 mg) resulted in a significant reduction in mean arterial pressure (-4.13; 95CI: -6.27 and -1.99; p = 0.000), but this reduction was not significant in the propranolol group (-2.27, 95% CI: -5.83 and 1.30; p = 0.204) at a median dose of 60mg/day (20-80mg). There was no significant difference between the 2 groups. These hemodynamic variations were well tolerated by our patients. This finding has been reported by numerous studies comparing carvedilol to propranolol. A recent study (Gupta, 2016), directly comparing carvedilol and propranolol in cirrhotic patients, showed a significant and large decrease in percentage change in MAP in carvedilol group compared to propranolol group (11.2±5.17 vs 7.8±4.16; p = 0.01) [14]. Sinagra et al in 2014 [18], comparing the hemodynamic effect of carvedilol and propranolol in cirrhotic patients, reported a significant mean reduction in MAP in the carvedilol group (-10.40; CI: -13.9 and -6.9) than propranolol (-6.66; CI: -10.17 and -3.15). According to Banares et al in 2002 [19], carvedilol resulted in an average reduction of MAP of -10.20 (CI: -17.56 and -2.84), while propranolol of -4.80 (CI: -15.51 and 5.91). Since patients taking carvedilol had a marked reduction in arterial pressure, orthostatic hypotension is to be expected. Carvedilol prescribed for hypotensive patients may be harmful to them, whether they are cirrhotic or non-cirrhotic. In our study, carvedilol showed a clear benefit in terms of heart rate reduction where the mean percentage change in HR was significantly high (16.08±5.29 vs 10.94±7.64; p = 0.0034), probably explaining this lower rebleeding in the carvedilol group.

In this series, there was no significant difference in drug tolerance in the two groups. A patient in the carvedilol group had experienced a severe side effect such as breathing difficulty forcing the patient to be withdrawn from the study. The majority of randomized studies comparing carvedilol to propranolol did not show any significant difference in terms of side effects between the two molecules. Gupta et al[14] found the same adverse effect profile between carvedilol and propranolol. Lo et al[13] showed that carvedilol had significantly fewer severe or moderate adverse events than the combination of nadolol and isosorbide mononitrate (8% vs. 38%; p<0.001). According to Yang et al[17], the total rate of adverse events was higher in the NSBB + EVL group than in the carvedilol + EVL group (OR: 0.39; 95% CI: 0.28–0.53; p=0.00001). Kim et al[20] did not show a difference between the carvedilol and propranolol groups on the incidence of drug-associated adverse events. Carvedilol is as well tolerated as propranolol, in primary and secondary prevention of cirrhotic or non-cirrhotic portal hypertension.

**Conclusion**

Carvedilol is as effective as propranolol in the prevention of variceal rebleeding in hepatic schistosomiasis. Our results showed less hemorrhagic recurrence in the carvedilol group than propranolol, but without significant difference. Despite the occurrence of an adverse reaction in one patient in the carvedilol group, the latter is as well tolerated as propranolol. Although a larger and long-term study is needed to support the results of this study, they hold promise for carvedilol.

**Abbreviations**
EVL: Endoscopic variceal band ligation; ALT: alanine aminotransferase; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; COPD: chronic obstructive pulmonary disease; AVB: atrioventricular block; CI: confidence interval; OR: odds ratio; NSBB: non-selective beta-blockers; GFR: glomerular filtration rate according to CKD-EPI.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the International Council for Harmonization Good Clinical Practice guideline and ethical principles reported in the 1996 version of the Declaration of Helsinki. Institutional and national ethical standards were followed in all procedures. Informed and signed consent was obtained in all from all participants. All authors had access to the study data and reviewed and approved the final manuscript before journal submission.

Consent for publication

Informed and signed consent was obtained in all from all participants.

Availability of data and materials

Data available on request from the authors: Data supporting the conclusions of this study are available from the corresponding author on reasonable request.

Competing of interests

The authors have no competing interests to declare.

Funding

This research has not received any specific grant from funding agencies in the public, commercial or non-profit sectors.

Authors’ contributions

CIR, LDER, DHHL and RR were the main contributors to drafting the manuscript. ASR, ALRR, THR and RMR critically reviewed the manuscript. SHR: Study design and critically reviewed the manuscript. All authors approved the final manuscript.

Acknowledgments

The authors would like to warmly thank the members of the Gastroenterology, Internal Medicine and Endoscopy Department of the Andrainjato Fianarantsoa University Hospital Center and Internal Medicine department of the Tambohobe Fianarantsoa University Hospital Center.
References

1. TchuemTcheunté L.A. Lutte contre la schistosomose : défi et perspective pour le XXIe siècle. Bull Soc Pathol Exot. 2006 ; 99 (5) : 372-76.

2. WHO. Schistosomiasis Progress Report. 2001–2011 and Strategic Plan 2012–2020. World Health Organization; Geneva: 2012.

3. El Tourabi H, El Amin AA, Shaheen M, Woda SA, Homeida M, Harron DWG. Propranolol reduces mortality in patients with portal hypertension secondary to schistosomiasis. Ann Trop Med and Parasitol. 1994;88(5): 493-500. http://dx.doi.org/10.1080/00034983.1994.11812896.

4. Klotz F. l’hypertension portale des schistosomoses : « une entité meurtrière ». Bull Soc Pathol Exot. 2003 ; 96(3) :191-95.

5. Rakotozafy JCR, Tanamasoandro R, Rakotoarimanana R, Raherimandimby H, Randriamamonjy F, Rasoloherimampionona MR et al. Schistosoma mansoni Infestation Rate Evaluation by Kato Katz’s Method in Haute Matsiatra Region (Madagascar) School Environment. International Journal of Prevention and Treatment 2016, 5(2): 22-24, https://dx.doi.org/10.5923/j.ijpt.20160502.02.

6. Abid S, Ali S, Baig MA, Waheed AA. Is it time to replace propranolol with carvedilol for portal hypertension? Word J Gastrointest Endosc. 2015; 7(5): 532-39. https://dx.doi.org/10.4253/wjge.v7.i5.532.

7. de Franchis R, Faculty BVI. Expanding consensus in portal hypertension: Report of the Baveno VI consensus Workshop: Stratifying risk and individualizing care for Portal hypertension. J Hepatol. 2015; 63 (3): 743-52. https://doi.org/10.1016/j.jhep.2015.05.022.

8. Pariente A. Should we leave propranolol for carvedilol to treat portal hypertension? Hépato Gastro 2013; 20: 385-90. https://www.jle.com/10.1684/hpg.2013.0867.

9. Tripathi D, Ferguson JW, Kochar N, Leithead JA, Therapondos G, McAvoy NC, et al. Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed. Hepatology 2009; 50: 825-33. https://doi.org/10.1002/hep.23045.

10. Shah HA, Azam Z, Rauf J, Abid S, Hamid S, Jafri W, et al. Carvedilol vs esophageal variceal band ligation in the primary prophylaxis of variceal hemorrhage: a multicenter randomized controlled trial. J Hepatol 2014; 60: 757-64. https://doi.org/10.1016/j.jhep.2013.11.019.

11. Reiberger T, Ulbrich G, Ferlitsch A, Payer BA, Schwabl P, Pinter M, et al. Carvedilol for primary prophylaxis for variceal bleeding in cirrhotic patients with haemodynamic non-response to propranolol. Gut 2013; 62 :1634-41. https://doi.org/10.1136/gutjnl-2012-304038.

12. Kiire CR. Controlled trial of propranolol to prevent recurrent variceal bleeding in patients with non-cirrhotic portal fibrosis. Br Med J 1989; 298: 1363-65. https://doi.org/10.1136/bmj.298.6684.1363.

13. Lo GH, Chen WC, Wang HM, Yu HC. Randomized, controlled trial of carvedilol versus nadolol plus isosorbide mononitrate for the prevention of variceal rebleeding. J Gastroenterol Hepatol 2012; 27: 1681-87. https://doi.org/10.1111/j.1440-1746.2012.07244.x.
14. Gupta V, Rawat R, Shalimar, Saraya A. Carvedilol versus propranolol effect on hepatic venous pressure gradient at 1 month in patients with index variceal bleed: RCT. Hepatol Int 2016. https://doi.org/10.1007/s12072-016-9765-y.

15. Stanley AJ, Dickson S, Hayes PC, Forrest EH, Mills PR, Tripathi D, et al. Multicentre randomized controlled study comparing carvedilol with variceal band ligation in the prevention of variceal rebleeding. J Hepatol 2014; 61: 1014-19. https://doi.org/10.1016/j.jhep.2014.06.015.

16. Malandris K, Paschos P, Katsoula A, Manolopoulos A, Andreadis P, Sarigianni M, et al. Carvedilol for prevention of variceal bleeding: a systematic review and meta-analysis. Ann Gastroenterol 2019; 32 (3): 287-97. https://dx.doi.org/10.20524/aog.2019.0368.

17. Jiao Yang, Ke Ge, Ling Chen and Jian-Le Yang. The efficacy comparison of carvedilol plus endoscopic variceal ligation and traditional, nonselective β-blockers plus endoscopic variceal ligation in cirrhosis patients for the prevention of variceal rebleeding: a meta-analysis. Eur J Gastroenterol Hepatol 31: 1518-26. https://doi.org/10.1097/meg.0000000000001442.

18. Sinagra E, Perricone G, D’Amico M, Tinè F, D’Amico G. Systematic review with meta-analysis: the haemodynamic effects of carvedilol compared with propranolol for portal hypertension in cirrhosis. Aliment PharmacolTher. 2014; 39 : 557-68. https://doi.org/10.1111/apt.12634.

19. Bañares R, Moitinho E, Matilla A, Garcia-Pagan JC, Lampreave JL, Piera C, et al. Randomized comparison of long-term carvedilol and propranolol administration in the treatment of portal hypertension in cirrhosis. Hepatology 2002; 36 : 1367-73. https://doi.org/10.1053/jhep.2002.36947.

20. Kim SG, Kim YT, Sohn JH, Um SH, Seo YS, Baik SK, et al. A Randomized, Multi-Center, Open-Label study to evaluate the efficacy of carvedilol vs. propranolol to reduce portal pressure in patients with liver cirrhosis. Am J Gastroenterol 2016; 111(11): 1582-90. https://doi.org/10.1038/ajg.2016.327.

Tables
Table 1
Demographic variables and baseline characteristics of patients

| Variables                                      | Propranolol Group (n = 30) | Carvedilol Group (n = 31) | p value |
|-----------------------------------------------|---------------------------|---------------------------|---------|
| Male (%)                                      | 21/30 (70%)               | 22/31 (70.97%)            | 0.934   |
| Age (years) (mean ± SD)                      | 44.33 ± 10.16             | 41.19 ± 10.73             | 0.246   |
| Grade of Esophageal Varix II/III             | 14/16                     | 14/17                     | 0.906   |
| Presence of red signs                        | 0/30                      | 0/31                      | 1.000   |
| Previous bleeding episodes 1/2/3/more than 3 | 9/10/7/4                 | 11/8/5/7                 | 0.669   |
| Ascites yes/no                                | 14/16                     | 25/6                      | 0.006   |
| Splenomegaly stage                           |                           |                           |         |
| - Middle stage                                | 2.86 ± 0.86               | 3.13 ± 0.99               | 0.275   |
| - Stage 1/2/3/4/5                            | 1/9/14/5/1               | 1/7/13/7/3               | 0.808   |
| Diameter of the portal vein                  |                           |                           |         |
| - ≤ 15 mm / > 15 mm                          | 7/18                     | 5/22                      | 0.418   |
| Presence of periportal fibrosis              | 25                       | 27                        | 1.000   |
| Platelets counts (G/L)                       | 2/17/11                  | 0/22/9                    | 0.270   |
| - ≤50 / 50–100 / >100                        |                          |                           |         |
| Bilirubin (µmol/l)                            | 30/0/0                    | 31/0/0                    | 1.000   |
| - < 35 / 35–50 / > 50                        |                          |                           |         |
| ALT (UI/l) ≤ 55                              | 30/30                     | 31/31                     | 1.000   |
| Albumin (g/l)                                 | 0/23/7                    | 0/24/7                    | 0.754   |
| - < 28 / 28–35 / > 35                        |                          |                           |         |
| Prothrombin activity (%)                     | 0/17/13                   | 0/18/12                   | 0.793   |
| < 40 / 40–60 / > 60                          |                          |                           |         |
| GFR > 60 ml/mn/1.73m²                        | 30/30                     | 31/31                     | 1.000   |
| Dose (mg/day) (median)                       | 60 (20–80)                | 12.5 (6.25–25)            | -       |

SD: standard deviation, ALT: Alanine aminotransferase, GFR: glomerular filtration rate according to CKD-EPI
Table 2
hemorrhagic recurrence, death occurrence and side effects

| Variables                        | Propranolol Group | Carvedilol Group | p value |
|----------------------------------|-------------------|------------------|---------|
| Hemorrhagic recurrence           | 3/30 (10%)        | 1/30 (3.33%)     | 0.301   |
| Time to recurrences bleeding (days) | 46.67 ± 42.52 (5/45/90) | 30             | 0.655   |
| Eradication of varices           | 0/30              | 2/28             | 0.150   |
| Decompensation occurrence       | 0/30              | 0/30             | -       |
| Death occurrence                 | 0/30              | 0/30             | -       |
| Side effects                     | 0/30              | 1/31             | 0.321   |
| - Breathing difficulty           | 0/30              | 1/31             | 0.321   |

Table 3
Hemodynamic parameters before and after treatment in the 2 groups

| Parameters                        | Propranolol Group (n = 30) | Carvedilol Group (n = 30) | p value |
|-----------------------------------|----------------------------|---------------------------|---------|
| HR at baseline (bpm)              | 70.30 ± 8.05               | 74.33 ± 7.40              | 0.048   |
| HR at 4 months (bpm)              | 62.27 ± 5.80               | 62.20 ± 5.43              | 0.964   |
| SBP at baseline (mm Hg)           | 112.33 ± 11.35             | 107.67 ± 11.04            | 0.112   |
| SBP at 4 months (mm Hg)           | 111.00 ± 7.59              | 101.97 ± 9.22             | 0.000   |
| DBP at baseline (mm Hg)           | 69.67 ± 9.28               | 65.33 ± 8.19              | 0.060   |
| DBP at 4 months (mm Hg)           | 66.67 ± 7.11               | 62.00 ± 4.84              | 0.004   |
| MAP at baseline (mm Hg)           | 83.70 ± 9.15               | 79.43 ± 8.18              | 0.062   |
| MAP at 4 months (mm Hg)           | 81.43 ± 5.76               | 75.30 ± 5.00              | 0.000   |

HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure
Table 4
Mean difference in hemodynamic parameters in the 2 groups at 4 months of treatment

| Parameters | Propranolol Group | Carvedilol Group | p value |
|------------|-------------------|------------------|---------|
|            | MD                | 95%CI            | p value | MD        | 95%CI       | p value |
| SBP (mm Hg)| -1.33             | -5.80; 3.13      | 0.546   | -5.70     | -9.03; -2.37| 0.002   |
|            |                   |                  |         | 0.114     |             |         |
| DBP (mm Hg)| -3.00             | -6.94; 0.94      | 0.130   | -3.33     | -5.99; -0.68| 0.016   |
|            |                   |                  |         | 0.886     |             |         |
| MAP (mm Hg)| -2.27             | -5.83; 1.30      | 0.204   | -4.13     | -6.27; -1.99| 0.000   |
|            |                   |                  |         | 0.363     |             |         |
| HR (bpm)   | -8.03             | -10.24; -5.82    | 0.000   | -12.13    | -13.92; -10.35| 0.000   |
|            |                   |                  |         | 0.005     |             |         |

HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, MD: mean difference, 95% CI: confidence interval