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ORIGINAL ARTICLE

Carvedilol *versus* propranolol in the prevention of variceal rebleeding in hepatosplenic schistosomiasis: Efficacy and safety

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Abstract

Background and Aim: Beta blockers combined with endoscopic variceal band ligation (EVL) is the most effective means for the prevention of variceal rebleeding. No data are available on the efficacy of carvedilol in the secondary prophylaxis of variceal bleeding in hepatosplenic schistosomiasis. The aim of this study was to evaluate the efficacy and safety of carvedilol compared to propranolol as secondary prophylaxis of variceal bleeding in hepatosplenic schistosomiasis.

Methods: This was a prospective, randomized study over a period of 14 months from February 2019 to March 2020. All patients with portal hypertension due to schistosomiasis with at least one episode of variceal bleeding were included and randomized to the propranolol and carvedilol groups. EVL protocol was continued in both groups.

Results: Sixty-one patients were eligible and randomized to propranolol ($n = 30$) and carvedilol ($n = 31$) groups. There was no significant difference in hemorrhagic recurrence between the carvedilol ($n = 1$) and propranolol ($n = 3$) groups (3.33 vs 10%; $P = 0.30$). At 4 months, there was a significant reduction in mean arterial pressure (−4.13 mm Hg; 95% CI: −6.27 to −1.99; $P < 0.05$) and heart rate (−12.13 bpm; 95% CI: −13.92 to −10.35; $P < 0.05$) in the carvedilol group. There was no significant difference between the groups on the mean difference in arterial pressure. One patient in the carvedilol group had breathing difficulty. There were no adverse events in the propranolol group.

Conclusion: There was no significant difference in the efficacy between carvedilol and propranolol. Carvedilol may be an alternative to propranolol for secondary prophylaxis of variceal rebleeding in hepatosplenic schistosomiasis.

Introduction

Schistosomiasis is a parasitic disease caused by trematodes of the genus *Schistosoma*. 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 frequent cause of portal hypertension, far ahead of viral hepatitis-induced cirrhosis or alcoholic cirrhosis.[3,4] In Madagascar, intestinal schistosomiasis (caused by *Schistosoma mansoni*) is a

real burden in certain regions including the Haute Matsiatra region, located south of Antananarivo.[5] Non-cirrhotic portal hypertension and gastrointestinal bleeding are complications of the infection caused by the intravascular parasitic trematodes *S. mansoni* and *S. japonicus*. A small subset of infected individuals in endemic regions develops the hepatosplenic form of the disease, which is characterized by presinusoidal portal block by egg embolization and periportal fibrosis.[1–4] Variceal hemorrhage is a major cause of morbidity in patients with non-cirrhotic portal hypertension in developing countries.[3] The utility of nonselective beta blockers (NSBBs) in the primary and secondary prevention of variceal bleeding in cirrhotic patients is well established.[6–10] In contrast to cirrhosis, published data on the effect of beta blocker therapy on schistosomiasis-related portal hypertension are scanty and contradictory. Propranolol was the first widely studied molecule in the prevention of esophageal varices bleeding during cirrhotic and non-cirrhotic portal hypertension (hepatosplenic schistosomiasis). Carvedilol is a NSBB with intrinsic anti-α_1-adrenergic activity.[6–11] Its effect on portal pressure is induced by β1-blockade, which reduces cardiac output, and β2-blockade, which elicits splanchnic vasoconstriction, and a reduction in intrahepatic resistance due to the α1-blocking effect.[6–20] However, up to 60% of patients do not achieve such reductions in hepatic venous pressure gradient (HVPG) after treatment with propranolol and face an increased risk of bleeding.[8,11,19,20] For propranolol nonresponders, carvedilol may still achieve a hemodynamic response rate as high as 56%.[11] Carvedilol decreases portal pressure more than propranolol.[8] Therefore, carvedilol is an alternative to propranolol. Furthermore, it is recommended for use together with propranolol in the primary prevention of variceal bleeding.[7] To our knowledge, no data is available on the efficacy and safety of carvedilol in the secondary prevention of variceal bleeding in hepatosplenic schistosomiasis. The objective of the present study was to evaluate the efficacy and safety of carvedilol *versus* propranolol in the secondary prophylaxis of variceal bleeding in hepatosplenic schistosomiasis patients.

Materials and methods

Study design. This was a prospective, randomized study within the Internal Medicine Department, University Hospital Tambohobe and the Hepato-Gastroenterology Department, University Hospital Andrainjato, Fianarantsoa, over a 14-month period from February 2019 to March 2020. All patients with hepatosplenic schistosomiasis presenting during the study period were screened for inclusion criteria. Patients were randomized in an alternating fashion. Patients were alternately divided into two groups: the carvedilol + endoscopic variceal band ligation (EVL) group and the propranolol + EVL group. The primary objective of the study was to compare variceal bleeding in the two groups at 4 months in patients with hepatosplenic schistosomiasis.

Study participants. All patients with non-cirrhotic portal hypertension due to schistosomiasis were screened for the following inclusion criteria: age >18 years, hospitalized for a first episode of variceal bleeding or presenting for EVL with history of variceal bleeding, and willing to give informed consent for participation in the study. Exclusion criteria were the following: refusal to participate in the study; suffering from liver cirrhosis; contraindications to beta blockers (asthma, chronic obstructive pulmonary disease, atrioventricular block, heart failure, bradycardia with HR ≤40 bpm, arteria hypotension with systolic blood pressure <90 mm Hg, peripheral arterial disease, uncontrolled diabetes); chronic kidney disease; pregnancy or lactation; or neoplastic disease.

The patients were free to leave the study at any time.

Methodology. Hepatosplenic schistosomiasis diagnostic criteria were the following: the presence of clinical signs (ascites, collateral venous circulation, splenomegaly); ultrasound signs (periportal fibrosis, portosystemic collaterals, enlarged portal vein >15 mm, splenic vein dilation ≥10 mm, and splenomegaly) and endoscopic signs (esophageal varices); and positive schistosomiasis serology.

Splenomegaly was classified according to Hackett's criteria (WHO, 1963) into five categories ranging from 0 to 5: spleen not palpable, even in deep inspiration, was classified 0; and spleen descending well below the umbilicus, exceeding the line passing between the umbilicus and the pubic symphysis was classified 5.

First episode of variceal bleeding was retained by the combination of several criteria: evidence of portal hypertension, presence of esophageal varices with red color signs or recent bleeding (hematemesis and/or melena), but no past history of upper gastrointestinal bleeding.

The patients with variceal hemorrhage (first episode or recurrence) were hospitalized and supportively cared according to a standardized protocol, and EVL sessions were scheduled every 4 weeks at discharge. EVL consisted of the placement of rubber rings on variceal columns, which are sucked into a plastic hollow cylinder attached to the tip of the endoscope by an experienced senior endoscopist. Ligation was started at the lower end of the esophagus and proceeded upwards in a spiral fashion. EVL was continued at 4 weekly intervals until the eradication of esophageal varices.

Patients with the first episode of variceal hemorrhage were randomized to the carvedilol group or propranolol group before the end of hospitalization. EVL sessions were initiated at discharge.

Patients with a history of outpatient variceal bleeding were randomized to the carvedilol or propranolol group at the time of hospitalization for EVL, and EVL protocols were continued in both groups.

The effectiveness of the beta blocker used was judged in the absence of variceal hemorrhage (hematemesis and/or melena) over a 4-month period. Safety assessment was judged based on the presence of side effects and the hemodynamic response.

In the case of severe side effects, beta blocker therapy was substituted with one that did not produce side effects.

Monitoring. The carvedilol group, after assessment of baseline heart rate (HR) and blood pressure, received a starting dosage of 6.25 mg daily, which was increased every 3 days up to a total daily dose of 25 mg, to achieve the target HR between 55 and 60 beats/min or a decrease in the HR by 25% from the baseline rate. The propranolol group, after assessment of baseline HR and blood pressure, received a starting dosage of 20 mg daily, which was increased every 3 days up to a total daily dose of 80–160 mg daily. Patients who were already on propranolol

retained the usual pre-EVL dose. The intake or resumption of the beta blocker treatment was started the day after EVL. Regular monitoring of the hemodynamic parameters and hemorrhagic recurrence was carried out at the time of inclusion, at the time of each EVL session (hospitalization), and at 15 days after each EVL session (outpatient consultation) until 4 months.

Statistical analyses. The data were recorded in predesigned formats and were statistically analyzed using the SPSS Statistics version 25 software. Data were expressed as means ± standard deviations (SD) and number (percentage) for nominal data. All *P*-values are two-tailed, with values <0.05 considered statistically significant. Comparison between two groups were performed using Student's *t*-test for parametric data and the Mann–Whitney *U*-test for nonparametric data. The chi-squared test (X^2) and Fisher's exact test were applied for categorical data analysis.

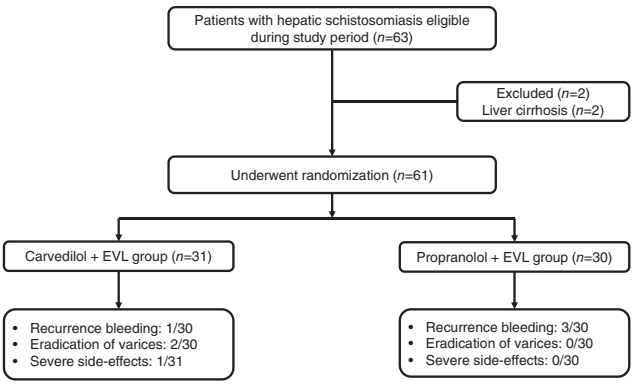

Figure 1 Flowchart of study.

Results

During the study period, a total of 63 patients experienced at least one variceal bleeding episode, of whom two were excluded (Fig. 1). Sixty-one patients were eligible and 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 variceal rebleeding was observed in the carvedilol group compared to the propranolol group (3.33 *vs* 10%) but without significant difference (Table 2). Hemorrhagic recurrence occurred after 30 days in the carvedilol group and after 5, 45, and 90 days in the propranolol group. We noted two eradications of esophageal varices in the carvedilol group and none in the propranolol group. There were no deaths in either group.

Effect on hemodynamic parameters. The median dose of propranolol to achieve a HR between 55 and 60/min was 60 mg/day (20–80 mg/day) and that of carvedilol was 12.5 mg/day (6.25–25 mg) (Table 1).

There was no significant difference between the two groups at baseline in HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) (Table 3). At 4 months of treatment, our results showed a significant reduction in the hemodynamic parameters in the carvedilol group (Table 4). This reduction was not significant between the two groups (propranolol *vs* carvedilol) except for HR (-8.03 *vs* -12.13; $P = 0.005$). The results were calculated as percentage changes. We found a significantly higher mean percentage change in HR in the carvedilol group than in the propranolol group (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

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/>3	9/10/7/4	11/8/5/7	0.669
Ascites, yes/no	14/16	25/6	0.006
Splenomegaly stage, means ± SD	2.86 ± 0.86	3.13 ± 0.99	0.275
Stage 0/1/2/3/4/5	0/1/9/14/5/1	0/1/7/13/7/3	0.808
Portal vein diameter (mm), ≤15/>15	7/18	5/22	0.418
Periportal fibrosis	25	27	1.000
Platelets counts (G/L), ≤50/50–100/>100	2/17/11	0/22/9	0.270
Bilirubin (μmol/L), <35/35–50/>50	30/0/0	31/0/0	1.000
ALT (U/L) ≤ 55	30/30	31/31	1.000
Albumin (g/L), <28/28–35/>35	0/23/7	0/24/7	0.754
Prothrombin level (%) <40/40–60/>60	0/17/13	0/18/12	0.793
GFR >60 mL/min/1.73 m^2	30/30	31/31	1.000
Dose (mg/day), median (extremes)	60 (20–80)	12.5 (6.25–25)	—

ALT, alanine aminotransferase; GFR, glomerular filtration rate according to CKD-EPI; SD, standard deviation.

Table 2 Hemorrhagic recurrence, death occurrence, and side effects

Variables	Propranolol group	Carvedilol group	*P*-value
Hemorrhagic recurrence (variceal rebleeding)	3/30 (10%)	1/30 (3.33%)	0.301
Time to recurrences bleeding (days)	46.67 ± 42.52	30	0.655
Eradication of varices	0/30	2/30	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 two 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

DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure.

Table 4 Mean difference in hemodynamic parameters in the two groups at 4 months of treatment

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

DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; MD, mean difference; SBP, systolic blood pressure; 95% CI, confidence interval.

patient in the carvedilol group experienced a severe side effect (breathing difficulty) and had to withdraw from the study. No patient in the propranolol group had any adverse effects (Table 2).

Discussion

Hepatosplenic schistosomiasis is the main cause of non-cirrhotic portal hypertension in endemic countries like Madagascar. In the late advanced schistosomiasis stage of the disease, the serious fibro-obstructive pathology leads to portal hypertension, ascites, hepatosplenomegaly, and, eventually, fatal hematemesis. Clinical pathology presents pipestem fibrosis and, indeed, much of the morbidity and mortality associated with schistosomiasis.[1–4] Hematemesis is the most common circumstance for the discovery of hepatosplenic schistosomiasis in Madagascar.[21] Secondary prevention of variceal bleeding remains essential.

Based on data from the existing literature, it appears that carvedilol has more potent desired physiologic effects than propranolol. The BAVENO VII Consensus recommends carvedilol for the primary prophylaxis of variceal hemorrhage.[7] A few trials comparing carvedilol with EVL for primary prevention have shown promising results in favor of carvedilol.[6,9,10] According to Reiberger, in cirrhotic patients, in primary prevention, carvedilol caused a reduction in HVPG in patients not responding to propranolol, resulting in fewer bleeding episodes with a 5% lower 2-year bleeding rate (*vs* 11% with propranolol and 25% with EVL; $P = 0.04$).[11] The combination of beta blockers and EVL is recommended of the prevention of variceal bleeding recurrence in patients with cirrhotic or non-cirrhotic portal hypertension.[7]

To our knowledge, the present study is the first to directly evaluate carvedilol *versus* propranolol as means of secondary prevention of variceal bleeding in hepatosplenic schistosomiasis. Despite its limitations, this study demonstrates a reduction in the incidence of variceal rebleeding in the carvedilol group compared to the propranolol group (3.33 *vs* 10%, $P = 0.30$). Numerous studies have demonstrated the efficacy of propranolol in secondary prevention during non-cirrhotic portal hypertension in terms of reducing the incidences of recurrent bleeding. Kiire showed that propranolol reduced the rate of hemorrhagic recurrence in patients with non-cirrhotic portal fibrosis compared with the

placebo group (5/25 *vs* 20/25; $P < 0.001$).[12] El Tourabi *et al.* in 2016 confirmed the results of Kiire (1/42 *vs* 8/40; $P < 0.02$).[3] There is limited evidence on the efficacy of carvedilol for the prevention of variceal rebleeding, and this evidence came from cirrhotic patients. The evidence for carvedilol in the prevention of variceal rebleeding is minimal but promising. Lo *et al.* in 2012 found that carvedilol is as effective in reducing hemorrhagic recurrence as the combination of nadolol and isosorbide mononitrate (51 *vs* 43%; $P = 0.46$).[13] Gupta *et al.* found in a cirrhotic population a similar proportion of recurrent bleeding between carvedilol and propranolol (1/30 *vs* 1/29; $P = 0.74$).[14] An interim analysis of a multi-center randomized controlled trial comparing carvedilol with EVL showed no significant difference in hemorrhagic recurrence (37.5 *vs* 29%; $P = 0.72$).[15] A meta-analysis including 13 studies with 1598 patients demonstrated the superiority of carvedilol over EVL in preventing variceal rebleeding.[16] A meta-analysis by Yang *et al.*, which included 802 patients (402 patients on carvedilol and 400 patients on propranolol), found carvedilol to be more effective than traditional NSBBs with a decrease in the rate of variceal rebleeding (OR: 0.53; 95% CI: 0.38–0.75; $P = 0.0003$).[17] The result of our 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-scale, long-term study would be needed to support and confirm this benefit in terms of variceal rebleeding in hepatosplenic 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 the mean arterial pressure (−4.13; 95% CI: −6.27 to −1.99; $P = 0.000$), but this reduction was not significant in the propranolol group (−2.27, 95% CI: −5.83 to 1.30; $P = 0.204$) at a median dose of 60 mg/day (20–80 mg). There was no significant difference between the two groups. These hemodynamic variations were well tolerated by our patients. A similar finding has been reported by numerous studies comparing carvedilol with propranolol. A recent study by Gupta in 2016, which directly compared carvedilol and propranolol in cirrhotic patients, showed a significant and large decrease in the percentage in MAP variation in the carvedilol group compared to the propranolol group (11.2 ± 5.17 *vs* 7.8 ± 4.16; $P = 0.01$).[14] Sinagra *et al.*, who compared the hemodynamic effect of carvedilol and propranolol in cirrhotic patients, reported a significant mean reduction in MAP in the carvedilol group (−10.40; 95% CI: −13.9 to −6.9) *versus* propranolol (−6.66; 95% CI: −10.17 to −3.15).[18] According to Bañares *et al.*, carvedilol resulted in a mean reduction in MAP of −10.20 (95% CI: −17.56 to −2.84), whereas propranolol resulted in a mean reduction of −4.80 (95% CI: −15.51 to 5.91).[19] Because patients taking carvedilol had a marked reduction in blood pressure, orthostatic hypotension would be expected. Carvedilol prescribed to hypotensive patients may be harmful to them, whether or not they are cirrhotic. In our study, carvedilol showed a clear advantage in terms of HR reduction over propranolol where the mean percentage change in HR was significantly high (16.08 ± 5.29 *vs* 10.94 ± 7.64; $P = 0.0034$), probably accounting for the lesser rebleeding in the carvedilol group.

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

We are aware of the limitations of the current study. The number of events in this study was too small to allow for a statistical difference, making the study underpowered. Another limitation of this study was the absence of the HVPG measurements.

In conclusion, there was no significant difference in efficacy between the carvedilol and propranolol groups. Carvedilol may be an alternative to propranolol for secondary prophylaxis of variceal rebleeding in hepatosplenic schistosomiasis. Despite the occurrence of an adverse event in one patient in the carvedilol group, it was as well tolerated as propranolol. Although a larger, long-term study is needed to confirm the results of this study, they are promising for carvedilol.

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Ethics statement

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 submission.

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

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