ejpmr, 2018, 5(11), 490-498

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

IMPACT OF NON-SELECTIVE BETA-BLOCKERS IN ADVANCED CIRRHOSIS

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Article Received on 20/09/2018 **Article Revised on 10/10/2018** **Article Accepted on 31/10/2018**

ABSTRACT

Background: Non-selective Beta-Blockers (BBs) are widely used in the prevention of variceal hemorrhage (VH). Their benefit has been demonstrated. However, are they safe in advanced cirrhosis? The aims of this study were first to assess the effectiveness of BBs on hemorrhagic risk in advanced cirrhosis and then to study the complications observed in these patients. **Methods:** We conducted a retrospective study that collects all Child-Pugh C cirrhotic patients followed in the Gastroenterology Department of Habib Thameur Hospital over a period of 45 months (July 2013-March 2017). These patients were divided into 2 groups according to whether they received BBs (Group 1 ; G1) or did not (Group 2 ;G2).The follow-up of these patients was specified in both groups and the effectiveness of BBs on the bleeding risk as well as possible complications were noted and compared. **Results:** Four hundred and twenty patients were included. Our study focused on 90 patients. The mean age at diagnosis was 56. The sex ratio (M/F) was 0,6. Most of cirrhosis were due to viral hepatitis C (30%). The first group included 68 patients (75,6%): 37 patients were under BBs in primary prevention of VH while 31 patients received the treatment in secondary prevention. In the 2nd group, BBs were not indicated in 15 patients, 4 patients had a contraindication such as asthma (N = 1), atrio-ventricular block (N = 2) and severe heart failure (N = 2). Three patients stopped BBs for poor tolerance. VH was observed in 25% of G1 patients and in 22,7% of G2 patients.It was observed in 16% of patients under BBs in primary prevention against 35%of patients under BBs in secondary prevention. For the other complications of cirrhosis, no impact of BBs was found on the occurrence of hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, refractory ascites and hepatocellular carcinoma. However, BBs significantly decreased the occurrence of decompensation by ascites (95% in G2 Vs 75% in G1, p = 0,019). In addition, they significantly improved the median survival time (72 months in G1 Vs 18,8 months in G2 , p<0,0001). **Conclusion:** According to our results, BBs are effective, do not generate more complications and are even protective since they significantly reduced the frequency of decompensation by ascites and improved survival. They should be pursued in the advanced stages of cirrhosis.

KEYWORDS: Cirrhosis, Beta-Blockers, Complications, Efficacy.

INTRODUCTION

Oesophageal varices bleeding is the leading cause of death during cirrhosis. The mortality can reach 30 to 50% without treatment and 10 to 20% with optimal management.[1] In this context, non-cardio-selective betablockers (BBs) are widely used for both primary and secondary prevention of varicoseal bleeding. The mechanism of action of these molecules is based both on the reduction of portal hypertension by reduction of cardiac flow by blocking cardiac B1 receptors and splanchnic vasoconstriction by blocking B2 splanchnic receptors. The prescription of this treatment has been well codified and its effectiveness has been proven in all stages of cirrhosis.[2]

But is the prescription of non-cardio-selective betablockers always effective and safe whatever the stage of cirrhosis?

Recently, the interest of BBs in advanced cirrhosis has been questioned. And so far, questions remain as to their benefits in balance to the risks and complications involved in cirrhotic patients especially in advanced or terminal stage of their disease.[3]

The objectives of our study are.

- To evaluate the effectiveness of non-cardioselective BBs on hemorrhagic risk in advanced cirrhosis.
- To describe the complications observed in patients with advanced cirrhosis treated with non-cardioselective BBs.

PATIENTS AND METHODS

A 45-month retrospective study including all cirrhotic patients hospitalized in the Gastroenterology Department of Habib Thameur Hospital during the period from July 2013 to March 2017 was performed.

Included patients were followed for cirrhosis regardless of etiology. The diagnosis of cirrhosis was based on clinical, biological, morphological and endoscopic arguments showing signs of hepatocellular insufficiency and portal hypertension.

The severity of cirrhosis was assessed by CHILD-PUGH score. Advanced cirrhosis was defined by Child Pugh C score (between C10 and C15).

Cirrhotic patients with CHILD PUGH A and B score, or who presented hepatocellular carcinoma, were not included.

Patients with a follow-up of less than 6 months, or not observant to the BBs treatment during the study were excluded.

For all patients, the epidemiological characteristics (age, sex, smoking habits, personal and family history, drug intake, hepatitis risk factors),data related to cirrhosis (circumstances of diagnosis, duration of follow-up, endoscopic data, need for variceal ligature or biological glue etiology, data relating to betablockers (nature of BBs, average dose as well as the duration of treatment in months, contraindications, reasons for discontinuation of treatment, evaluation of the effectiveness of the treatment) were specified.

Patients were divided into two groups according to whether they were treated by BBs or not. During the follow-up, the complications occured were noted and compared between the two groups: digestive bleeding, hepatic encephalopathy, spontaneous infection of the ascites liquid, decompensation of the cirrhosis, refractory ascites, hepatorenal syndrome or degeneration.

Finally, the survival was specified, as well as the cause of death.

Statistical analysis was performed by the SPSS Software. Descriptive and analytical study were performed. Survival analysis was performed according to the Kaplan-Meier method starting from a 100% survival at baseline. A patient was censored if he deceaded or lost of view of during the follow-up. Prognostic factors were searched by the Log-Rank test.

RESULTS

Descriptive study

During the study period, 420 cirrhotic patients were hospitalized in our department. 320 (76% of the cases) had a Child-Pugh A or B score and were not eligible. Only 100 patients (24% of cases) had a Child-Pugh-Pugh C score. Among patients with a Child-Pugh C score, two were not included because they had hepatocellular carcinoma. Five patients were excluded because of follow-up period of less than 6 months and three patients were non-observant for BBs treatment. Than, 90 cirrhotic patients with a Child-Pugh C score were included.

Patients were divided into two groups according to whether betablockers were taken or not:
- Group 1 (G1): Patients receiving BBs.
- Group 2 (G2): Patients not receiving BBs.

The first group included 68 patients (75.5%) while the second group included 22 cirrhotic patients (24.5%). The distribution of patients is summarized in Figure 1.

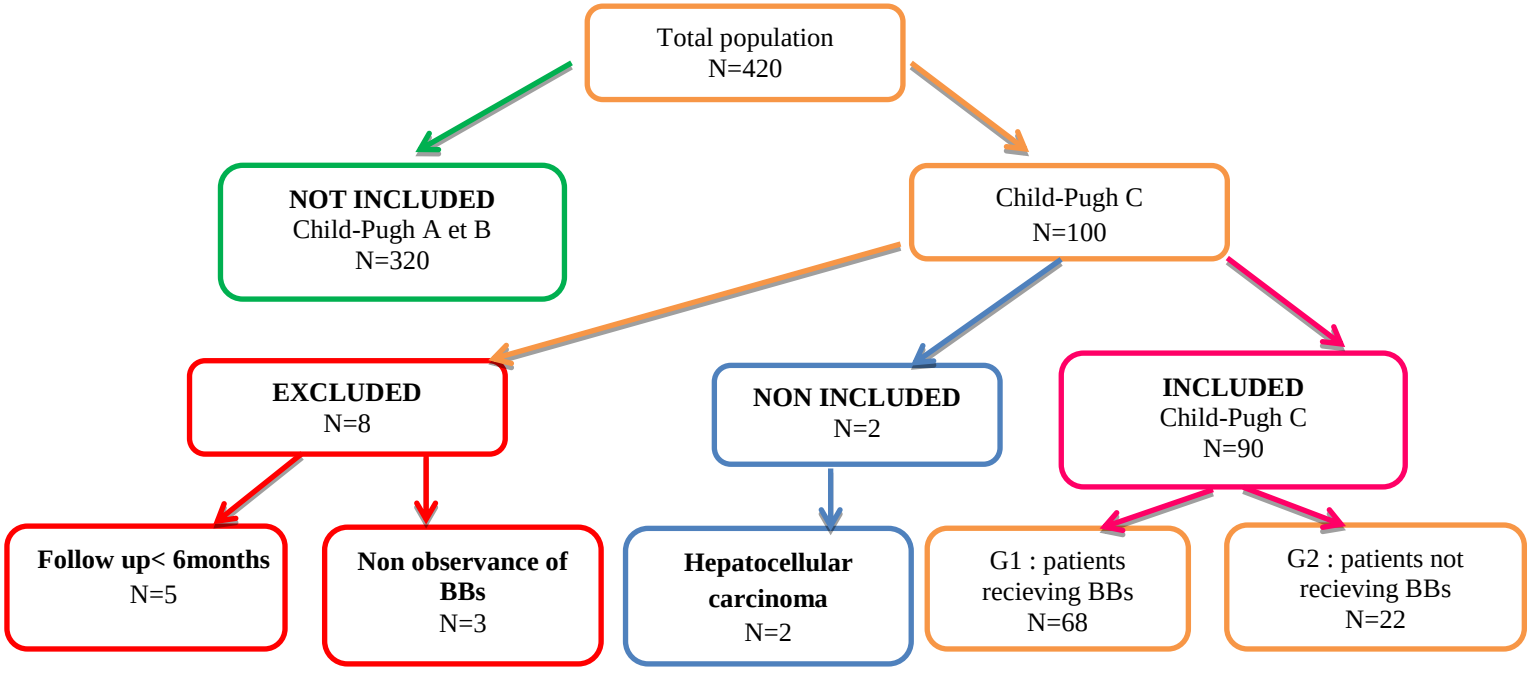

Figure 1: Distribution of the study population.

Mean age was 56 years and sex ratio (M / F) was 0.6. Twenty-seven patients were smoking (30%).

Most patients had at least one comorbidity associated with cirrhosis (64.4%) and diabetes was the leading comorbidity in both groups.

Viral hepatitis was the most common cause of cirrhosis in our series dominated by hepatitis C found in 29% of cases (27 cases) followed by hepatitis B in 23% of cases (21 cases). Viral origin was predominant in both groups: it was 60% in G1 and 32% in G2, with a predominance of hepatitis C. Other etiologies included autoimmune hepatitis, primitive biliary cirrhosis, alcoholic and non alcoholic steatohepatitis found in 17%, 7%, 5% and 3% respectively.

Average duration of follow-up was 63 months (72 months in the 1st group and 19 months in the 2nd group). Endoscopic signs of portal hypertension were present in 100% in G1 and 63% in G2.

All patients were classified CHILD C (mean 11.38) with a mean CHILD score of 11.4 in group 1 and 11.5 in group 2.

All patients in the first group were on Propranolol with an average dose of 54.2 mg / day.

The average duration of treatment was 49 months. Among them, 37 (54%) received BBs in primary prevention while 31 (46%) received them in secondary prevention associated with endoscopic band ligation.

Concerning the second group, 15 (68%) had no indication for initiation of treatment, 4 (18.1%) had a contraindication (severe heart failure in one case, 2nd and 3rd degree atrioventricular block in two cases and asthma in one case) and 3 (13.9%) stopped the treatmend for intolerance (severe asthenia in 1 case and hypotension in 2 cases). Figure 2 summarizes the previous data.

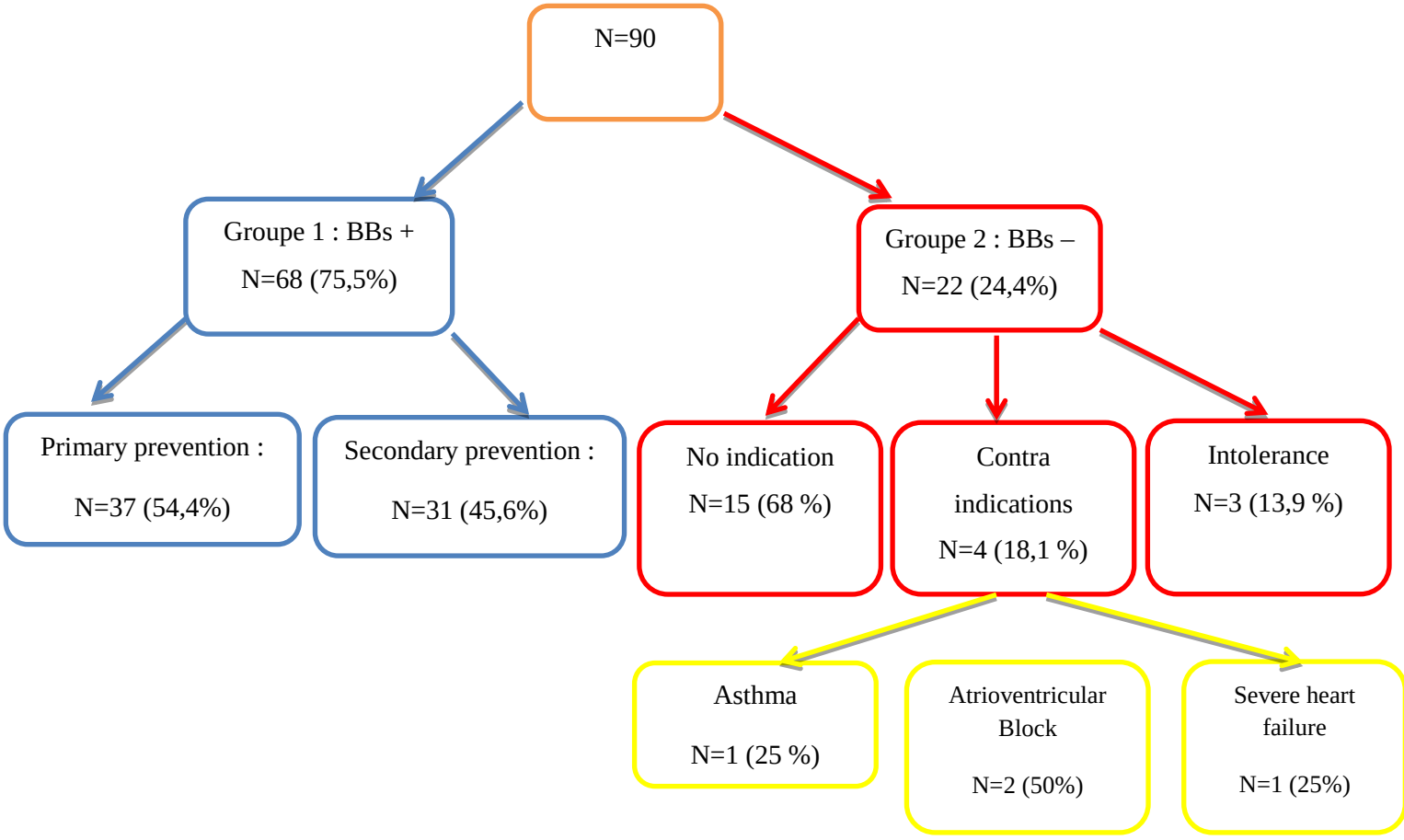

Figure 2: Distribution of patients according to beta-blocker intake.

Mean systolic blood pressure was 113 mmHg [89-140 mmHg] in patients treated with BBs versus 111.5 mmHg [90-130 mmHg] in patients who did not receive BBs.

Mean diastolic blood pressure was 67.5 mmHg in G1 patients [50-80 bpm] versus 94.5 mmHg [50-80 mmHg] in G2 patients. Mean blood pulse rate was was 68 bpm after BBs [56-92 bpm] in G1 and 78 bpm in G2 patients [64-94 bpm].

Throughout the period of our study, complications of cirrhotic disease were noted in all patients.

Gastrointestinal bleeding occurred in 22 patients in our series (24.4%). It was fatal in four patients. The origin was oesophageal in 17 cases (77% of cases of HD) and gastric in five patients (23% of cases).

The occurrence of bleeding was observed respectvely in 17 patients of group 1 (25%) of and 5 patients of group 2 (22.7%).

Hepatic encephalopathy was observed in 37 patients of our series i(41% of cases). It was noted in 25 patients in group 1 (36.7%) and 12 patients of group 2 (54.5%).

A spontaneous bacterial peritonitis occurred in 23% of patients in our series (N = 21). It was observed in 17 patients in group 1 i(25%) compared to four patients of group 2 (18%).

A hepatorenal syndrom was objectified in 23 patients of our series (25.5%). It was noted in 26.5% of G1 patients (N = 18) versus 22.7% of G2 patients (N = 5). In all cases, the hepatorenal syndrom was type 2.

The mean time to onset of hepatorenal syndrom compared to the diagnosis of cirrhosis was 59.6 months [3 -186 months] in G1. This delay was shorter in patients without BBs with an average of 7.6 months [4 - 14 months]. The mean value of creatinine was 152.16 µmol / L in G1 versus 241 µmol / L in G2.

An oedemato-ascitic decompensation or an increase in ascites already present occurred in 72 patients throughout the follow-up period (80%).

Fifty-one (or 75%) of group 1 patients had at least one ascitic decompensation of their disease.

Refractory ascites developed in 33 patients in our series (37% of cases). In the majority of cases, the occurrence of a type 2 hepatorenal syndrom was the cause of refractory ascites (N = 22, 24.5% of cases).

During the follow-up period, hepatocellular carcinoma was detected in 21 patients. Eighteen patients of group 1 (26%) developed HCC. It was a small HCC in four patients and a multifocal HCC in the others. Three patients in the second group (13.6%) developed a HCC during their follow-up. CHC was multifocal in all cases. No patient was suitable for curative treatment due to the advanced stage of cirrhosis.

Overall mortality rate was 44% in our population. Mean survival was 59.18 months with extremes ranging from 8.6 months to 87.7 months.

The mortality rate in patients with BBs was 38.2% versus 63.6% of patients without BBs.

Mean survival in G1 was 72.23 months [56.7 - 87.7 months]. It was shorter in patients of the 2nd group with an average of 18.86 months [8.6 - 29 months].

In patients with BBs, the main cause of death was hepatocellular carcinoma found in 34.6% of cases (N = 9), followed by severe sepsis and gastrointestinal bleeding both found in 15.4% cases (N = 4 each). Hepatic encephalopathy led to death in 4% of cases (N = 1).

Concerning patients in the 2nd group, the death was secondary to severe sepsis in 21.5% of cases (N = 3), hepatoci encephalopathy in 21.5% of cases (N = 3), multifocal hepatocellular carcinoma in 14% of cases (N = 2) and gastrointesinal bleeding in 14% of cases (N = 2).

Figure 3 summarizes and compares the causes of death for both groups of patients.

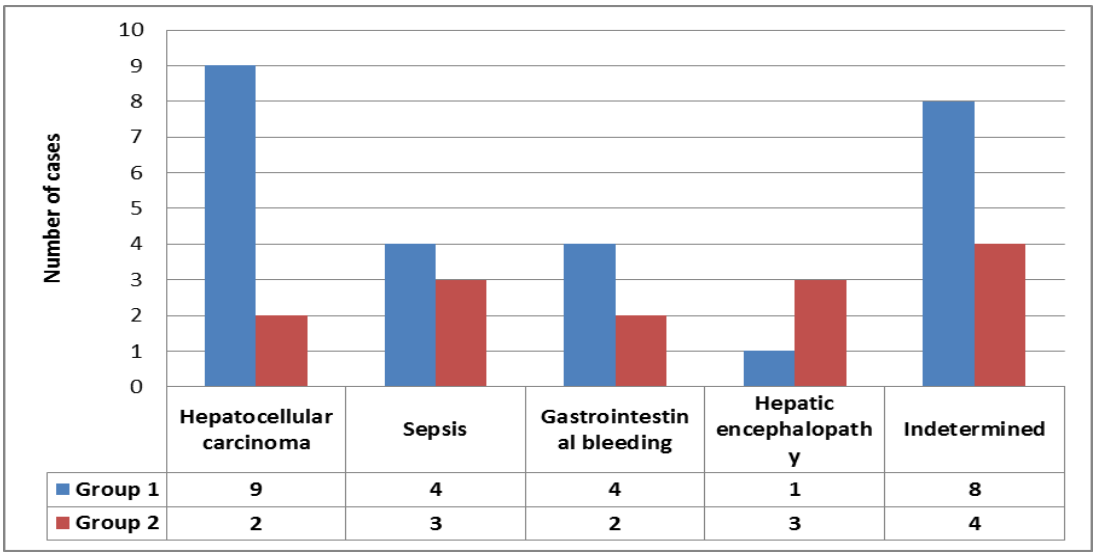

Figure 3: Causes of death in groups G1 and G2.

Analytical study of the studied population

The two groups of patients were epidemiologically comparable (age and sex).

Diabetes was the most associated comorbidity in the first group (38% of G1 patients) followed by hypertension (26% of G1).

Comparing the two groups, the duration of follow-up of patients with BBs was greater than that of patients who did not receive BBs (72 months in G1 versus 19 months in G2). This difference was statistically significant (p = 0.001).

Etiologically, the viral origin and more precisely post-viral C predominated in both groups without significant difference.

Endoscopic signs of http were present in all the patients of the first group (N = 68, 100% of G1) against 63% only of the patients of the 2nd group. This difference was statistically significant with p = 0.001.

As for the distribution of patients according to Child-Pugh's scrore, it was homogeneous and comparable in both groups.

Gastrointestinal bleeding occurred in 25% of patients with BBs versus 22.7%. This difference was not statistically significant (p = 0.53).

Comparison of complications of cirrhosis in both groups is resumed in Table 1.

Table 1: Comparison of the occurrence of the various complications of cirrhosis in G1 and G2.

	G1 (%)	G2 (%)	p
Complications	94	100	0,56
Spontaneous bacterial peritonitis (SBP)	25	18	0,45
Number of SBP	1,53	1,25	0,2
Oedematoascitic decompensation	75	95,5	**0,019**
Hepatorenal syndrom	26,5	22,7	0,48
Hepatic encephalopathy	36,7	54,5	0,21
Refractory ascites	38,2	32	0,46
Hepatocellular carcinoma	26	13,6	0,53

The impact of BBs on survival was also studied: Overall survival was 59 months. Mean survival in patients receiving BBs was 72 months compared with 18.8 months in patients of the second group, p <0.001.

Figures 4 and 5 respectively illustrate the overall survival and impact of BBs on survival in both groups of patients.

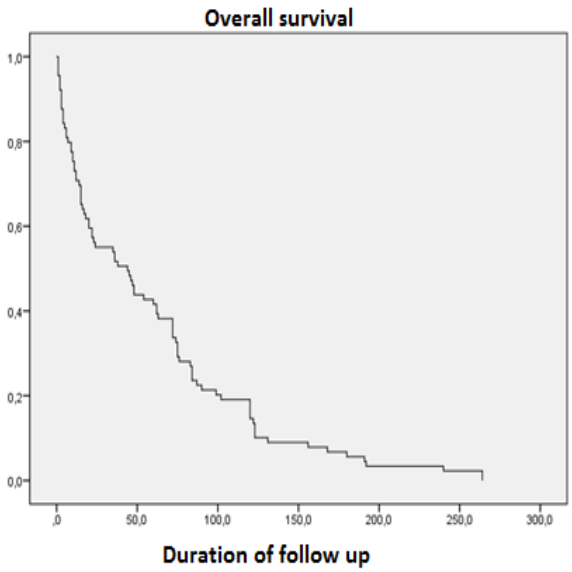

Figure 4: Overall Survival of the Study Population.

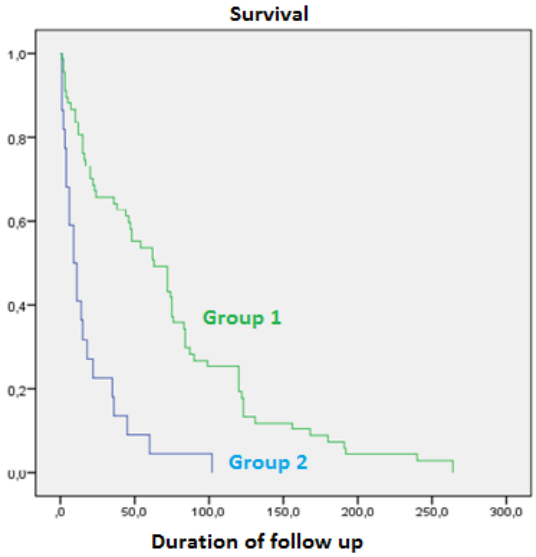

Figure 5: Impact of BBs on survival in Group 1 and Group 2.

DISCUSSION

Our study results demonstrate a positive impact of BBs in advanced cirrhosis attested by a longer survival and a lower risk of decompensation.

Our study has some weaknesses mainly due to methodological limitations. Its retrospective nature can cause a bias in the collection of information. Nevertheless, the lack is weighted by the standardization and objectivity of the collection of information.

In addition, the monocentric nature of the study may be a selection bias but has been avoided as much as possible by the use of reliable and accurate diagnostic criteria.

Similarly, the representative character of the cases compared to the controls could not be respected due to the small percentage of patients without BBs at this stage of the disease.

Also, Child-Pugh C score was choosen to define the advanced nature of cirrhosis because this score is widely validated and easy to use.[4] However, Child-Pugh score suffers from some limitations. Its disadvantages are particularly related to the subjective character of the assessment of the importance of ascites and the stage of hepatic encephalopathy. On the other hand, this score suffers from a ceiling effect. Indeed, the level of bilirubin is not discriminating above 50µmol / l. Thus patients with bilirubin at 60 or 200 µmol / l will have the same number of points while their prognosis is clearly different.

It should be noted that all patients were classified Child-Pugh C at the time of their inclusion but the follow-up does not provide information on the evolution of this score during our study, especially after etiological treatment of cirrhosis (antiviral therapy).

Our study has however several strengths. This is a large-scale study that involving a homogenous population with a good follow-up and very strict inclusion and exclusion criteria and no patient was lost of view. The results of the statistical tests were reliable and consistent conclusions could be drawn.

On the other hand, our study interested in a delicate subject, which is still at the origin of multiple questions in literature.

In addition to their well-known cardiovascular effects[5], BBs have been used for years by hepatologists in cirrhosis. Their beneficial effect is certain and has been established since 1981 in the prevention of gastrointestinal bleeding.[6] Their effects in advanced cirrhosis were studied later. Indeed, it was in September 2010 that appeared in the journal Hepatology, a prospective observational study evaluating the effect of BBs on the survival of 151 cirrhotic patients with refractory ascites. This study concluded that, in multivariate analysis, prescribing BBs in this category of patients remains an independent predictor of mortality in the same way as hepatocellular carcinoma.[3]

It is in this context that the BAVENO VI guidelines in 2015, set some restrictions on the use of BBs in cirrhosis at the stage of refractory ascites.[2]

Our results are in agreement with those of the literature[8] for the prevention of gastrointestinal haemorrhage. Indeed, a meta-analysis made by D'Amico G and Al in 1999, demonstrated that the reduction of gastrointesinal bleeding risk was significantly reduced in decompensated cirrhosis: this meta-analysis included 4 controlled studies with 305 patients with decompensated cirrhosis: the risk of bleeding at 2 years was 22% in patients with BBs compared to 31% in the control group with no significant difference.[7]

For the primary prevention of HD, the impact of BBs was assessed by a large Franco-Italian multicenter meta-analysis of four randomized controlled trials involving 589 patients: 286 of them were under BBs Vs 303 under placebo.[9] This meta-analysis demonstrated that lower rates of gastrointesinal bleeding were observed in cirrhotic patients under BBs with or without ascites and this regardless to the Child Pugh score.

For secondary prevention of HD, another meta-analysis including 12 randomized trials and 389 patients found a significant reduction in gastrointestinal bleeding occurrence and death in patients with advanced cirrhosis under BBs but this effect on survival has not been found in patients with moderate cirrhosis.[10]

The results of these two meta-analyzes suggest that the benefits of BBs in patients with more severe disease is higher.

Our study did not find a statistically significant relationship between BBs and the occurrence of hepatic encephalopathy (p = 0.21). However, it appears that BBs may prevent worsening of hepatic dysfunction because the prevalence of hepatic encephalopathy was higher in the untreated group:f 36.7% in G1 versus 54.5% in G2.

The effect of BBs on the occurrence of hepatic encephalopathy has not been much studied certainly because it is rather related to the hepatocellular insufficiency than to the protal hypertension. The team of Hernandez and Al[11] showed that patients under BBs and more specifically those with a hemodynamic response to treatment would have less hepatic encephalopathy than patients without BBs and patients under BBs but without a hemodynamic response. But this difference was not significant (16% vs 6% at 2 years, p = 0.14) and the effective was small (N = 83).

Betablockers would protect against the occurrence of spontaneous bacterial peritonitis. This hypothesis was verified by the American team of Juan Turnes in 2006[12] by conducting a retrospective study controlled over 8 years including 71 patients. The reduction in the risk of spontaneous bacterial peritonitis was significant in the Nadolol group. A 2009 meta-analysis by Senzolo and Al on a total of 644 patients with no history of spontaneous bacterial peritonitis $who were not on primary antibioprophylaxis found a significant difference (p = 0.001) in favor of BBs with OR = 0.42.[13]

In our series, this hypothesis was not confirmed and no significant difference was found between the two groups of patients as well for the prevalence (p = 0.45), as for the average number of episodes of infection (p = 0.2).

It has been widely demonstrated in the literature that BBs are correlated with a decreased risk of hepatorenal syndrom.[11,13,14] But in recent years, new studies have questioned the safety of this drug on kidney function in advanced cirrhosis in particular. This is the case of a retrospective study performed by Mondorfer and Al[15] in 2014 including 607 patients. This study demonstrated that a greater proportion of BBs patients develop SHR compared to those who were not on treatment (24% vs 11% in patients without BBs, p = 0.021).

Our study did not show any effect of BBs on the occurrence of hepatorenal syndrom.

Concerning refractory ascites, our study objectified a prevalence of 38.2% in G1 and 32% in G2 without significant difference. While browsing the literature, we found no evidence of studies assessing the relationship between the use of this treatment and the development of refractory ascites.

The protective effect of non-cardioselective BBs has already been demonstrated for epithelial ovarian cancers in a large-scale, multicentre study involving 1425 women with ovarian cancer.[16] The authors found that the use of non-cardioselective BBs was associated with significantly improved survival (38.2 months vs 90 months, p <.001). Other studies have also shown such effects in breast cancer[17], pancreatic cancer[18] and men with prostate cancer.[19] In view of the results of these studies, authors are interested in the effects of this drug on the risk of hepatocellular carcinoma in cirrhosis. Nkontchou and Al[20] conducted a prospective study of 291 patients with post-viral cirrhosis C who were closely screened for hepatocellular carcinoma in cirrhosis. The incidence at 3 and 5 years was 4% and 4%, and 10% and 20%, respectively, in patients treated and not treated with BBs. In multivariate analysis, Propranolol was associated with a significant decrease in the risk of developing hepatocellular carcinoma. Pathophysiologically, BBs act by two mechanisms to limit developpement of cancer: first by decreasing hepatic inflammation[21,22], then by blocking angiogenesis.[23-24]

In our work, we did not find any impact of BBs on hepatocellular carcinoma. The incidence was respectively 26% and 13.6% in group 1 and 2, p = 0.53.

Finally, BBs may have major anti-inflammatory role in advanced cirrhosis by reducing systemic inflammation, thereby preserving vascular endothelium, which improves systemic perfusion.[25] This hypothesis was confirmed by the Anderson and Al study conducted in 2016 on a group of 38 patients with decompensated, advanced cirrhosis (Child-Pugh average score of 10). This work found a significantly lower rate of white blood cells in patients under BBs, and a better hemodynamic profile in these patients with less vasodilatation. This better hemodynamic profile was correled to the reduction of systemic inflammation in BBs patients.[26]

Recent studies have suggested that end-stage BB use of cirrhosis is associated with increased mortality in these patients.[3,27] On the other hand, other studies have shown that the use of BBs can be beneficial in this same category of patients by decreasing bacterial translocation and thus improving survival.[28]

A unicentric prospective study conducted by the Sersté et al[3] team in 2010 evaluated the effect of BBs administration on survival in patients with refractory ascites. The mean survival was 20 months in patients without BBs versus 5 months in Propranolol patients, p = 0.0001. Among the independent mortality factors found, in addition to the Child-Pugh C score, hyponatremia, and renal failure as a cause of refractory ascites, BBs were also found in multivariate analysis.

Since the publication of this study, doubt about the effect of BBs on survival has attracted the interest of several teams. This is the case of Mondorfer and Al who have demonstrated that taking BBs in patients with a history of spontaneous bacterial peritonitis significantly reduces survival..[29]

It is in the face of these controversial results that the concept of "Therapeutic Window" was launched by the Krag team.[29] According to this study, since cirrhosis has several phases BBs prescription should follow the evolution of the disease and be limited to specific stages of the disease.

Nevertheless, this "closure of the therapeutic window of BBs" has recently been questioned. In a cohort of 322 patients with decompensated cirrhosis on the waiting list for liver transplantation, Leithead and Al[27] found that BBs reduce mortality. Aday and Al in 2016 concluded that the use of non-cardioselective BBs provides significant benefit for survival regardless of the stage of cirrhosis, even in the presence of ascites.[30]

Moreover, in a large multicenter randomized controlled trial involving 1,188 patients with decompensated cirrhosis, Bossen et al[31] found no difference in mortality at 52 weeks between BBs and non-BB patients. Finally, Moonkerjee and Al[32], showed a 28-day mortality rate significantly lower in patients with BBs compared to those who were not (24% vs 34%, p = 0.048). In addition, patients with BBs had less severe acute hepatic impairment with slower progression compared with the control group.

According to the results of these latest studies, the use of BBs should be maintained if indicated regardless of the stage of cirrhosis.[33] Moreover, in the latest recommendations of Baveno VI[2], the use of BBs in primary or secondary prevention of gastrointestinal bleeding is indicated in all stages of the disease. Their suspension at the stage of refractory ascites is recommended only in 3 situations: hypotension with

PAS <90 mmHg, hyponatremia <130 mmol / l or acute renal failure.

CONCLUSION

In conclusion, other prospective and multicenter studies are probably needed to evaluate the impact of BBs depending on the stage of cirrhosis.

Given the results of our study, it seems imperative to keep cirrhotic patients under BBs even at an advanced stage of their disease, exceptied if there are contra indications and major side effects. This was recommended at the 6th BAVENO Consensus Conference and discuss their discontinuation was recommended only if one of these criteria is present: systolic blood pressure <90 mmHg, hyponatremia <130 mmol / l or in case of acute renal failure. Apart from these situations, the place of BBs in these patients remains unavoidable.

In addition, regarding the recently discovered beneficial effects of BBs on the prevention of hepatocellular carcinoma by decreasing hepatic inflammation and blocking angiogenesis, other studies may be interesting in this topic. . If this hypothesis is confirmed, BBs could be prescribed at an earlier stage of the disease regardless of the severity of the portal hypertension thus preventing gastrointestinal bleeding and hepatocellular carcinoma. It would then be the first preventive treatment for hepatocellular carcinoma.

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