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NONSELECTIVE BETA-BLOCKERS IN PRIMARY PROPHYLAXIS OF ESOPHAGEAL VARICEAL BLEEDING IN PATIENTS WITH ASCITES WAITLISTED FOR LIVER TRANSPLANTATION

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Objective: to determine the efficacy of non-selective beta-blockers (NSBBs) in the primary prevention of bleeding esophageal varices and to assess their impact on the survival of patients with ascites enrolled in the liver transplant waiting list (LTWL). **Materials and methods.** We carried out a retrospective comparative study of cirrhotic patients with severe ascites and esophageal varices without bleeding before enrollment in the LTWL. Primary prophylaxis of variceal bleeding included the use of NSBBs (n = 97, group 1). These drugs were not used in the other patients (n = 91, group 2). **Results.** There were no significant differences between the groups in terms of clinical, laboratory and demographic parameters, MELD scores and Child–Turcotte–Pugh (CTP) classes for cirrhosis. Patient groups included in the study had no significant differences with respect to incidence of medium- and large-sized varices and incidence of severe ascites. Bleeding incidence was significantly lower in the NSBBs group than in the non-NSBBs group (52.6% and 95.6%, respectively, p = 0.0001). **Conclusion.** NSBBs constitute an efficacious therapy in primary prophylaxis of esophageal variceal bleeding, thereby saving life and preventing delisting of patients with ascites from the LTWL.

Keywords: liver transplant waiting list, ascites, bleeding, nonselective beta-blockers.

INTRODUCTION

Clinically significant portal hypertension (CSPH) causes the transition of liver cirrhosis from a compensated to a decompensated stage, characterized by severe complications like ascites, variceal bleeding, gastric variceal bleeding, hepatic encephalopathy (PE) [1–3]. Development of decompensated cirrhosis is an indication for inclusion of patients into the liver transplant waiting list (LTWL) [1]. Despite the undoubted successes of liver transplantation (LTx), characterized by an increase in the number of saved patients, Russia and the world at large are experiencing the problem of donor organ shortage, and, as a consequence, increased waiting time for liver transplantation in patients with decompensated cirrhosis [4–6].

Increased waiting time for LTx causes high risk of mortality due to CSPH progression and developing complications, which predetermines the urgent task of saving lives and preventing attrition of patients from the LTWL [1, 7]. The International Consensus on the Management of CSPH Patients (Baveno VII) recommends that patients with ascites and medium-large varices (≥5 mm) with Child–Turcotte–Pugh class C be submitted to primary prophylaxis of bleeding with either nonselective beta-blockers (NSBBs) or endoscopic variceal ligation (EVL) in order to reduce mortality. The Baveno VII guidelines recommend the use of traditional NSBBs or carvedilol for the prevention of the first bleeding episode in this category of patients, reserving a place for EVL for patients with intolerance, or with contraindications to the use of beta-blockers [1].

MATERIALS AND METHODS

Included in a retrospective comparative study conducted at the Center for Surgery and Donor Coordination, Rostov Regional Clinical Hospital, after obtaining approval from the local ethics committee, were 188 patients with decompensated cirrhosis of viral and alcoholic etiology.

The inclusion criteria were: absence of variceal bleeding before inclusion in LTWL, ascites of varying severity, alcohol abstinence confirmed by narcologist reports for at least 3 months before inclusion in LTWL in patients with alcohol-induced cirrhosis.

Exclusion criteria: patients with hepatocellular carcinoma or other malignant diseases accompanied by ascites.

The first group of patients consisted of 97 patients who underwent primary prophylaxis of variceal bleeding

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using NSBBs, the second group consisted of 91 patients who received no NSBBs for various reasons (intolerance, contraindications).

The primary endpoint of the study was to determine the efficacy of NSBBs in the primary prevention of esophageal bleeding in the compared groups.

The secondary endpoint of the study was the study of patient survival in the compared groups.

Demographic, clinical, and laboratory parameters were obtained from a continuously updated electronic database of patients who were in LTWL for 1 to 36 months awaiting LTx. In the case of a stable state, clinical and biochemical blood tests and hemostasis indicators were repeated at 3-month intervals. The following indicators were calculated: MELD-Na [8] and Child–Turcotte–Pugh (CTP) [9, 10].

Screening esophagogastroduodenoscopy (EGD test) was performed in patients with ascites to detect varicose veins with high risk of bleeding (medium- and large-sized nodules) according to the recommendations of Baveno VI, Baveno VII (1, 11) and the World Gastroenterology Organisation (WGO) [12]. The severity of ascites was determined according to the International Ascites Club expert criteria [13].

Abdominal ultrasound was performed during initial examination of patients and every 6 months after LTx.

Group 1 patients received carvedilol (n = 46), propranolol (n = 36), and nadolol (n = 15). The initial carvedilol dose was 6.25 mg/day and the maximum dose was 25 mg/day; propranolol 40 mg/day and 240 mg/day, respectively. The initiating nadolol dose was 40 mg/day and the maximum dose was 80 mg/day. Administration of NSBBs was accompanied by monitoring of heart rate and blood pressure; the drug dose was adjusted whenever these parameters decreased. Patients in both groups received diuretics; paracentesis was performed if ascites was resistant to diuretics. Patients with HBV and HCV-associated cirrhosis received antiviral therapy with nucleoside analogues and a combination of direct-acting antivirals, respectively.

Data obtained was analyzed using the statistical program IBM SPSS Statistics (version 23). The Kolmogorov–Smirnov test was used to check the normality of distribution of the obtained values of data samples. Data with a normal distribution of values was represented by arithmetic mean (M) and standard deviation (SD). Significance of differences between the compared values in the case of normal distribution was determined by Student's t-test. In the absence of normal distribution, nonparametric criteria were used: Wilcoxon for pairwise comparisons of dependent variables, Mann–Whitney U test, and Pearson's chi-square test for comparisons of independent variables. Quantitative data with non-normal distributions was expressed as median (Me) and interquartile range (IQR, the interval between the 25th and 75th percentiles). Frequency and percentage (%) analysis was used to evaluate qualitative data. A p value <0.05 was taken as the threshold criterion for statistical significance between compared indicators. The effectiveness of primary prophylaxis of variceal bleeding (percentage of non-bleeding patients) and survival of patients in the compared groups (with and without NSBBs) were determined by Kaplan–Meier estimate with calculation of logarithmic Log-Rank (Mantel–Cox) test that determines differences between the corresponding curves.

RESULTS

Table 1 and Table 2 present data on demographic, clinical, laboratory parameters, and indicators (MELD-Na, CTP) in the groups of patients with ascites who received NSBBs (n = 97) and who did not receive NSBBs (n = 91) while waiting for LTx.

Table 1

Comparative characteristics of indicators of NSBB and non-NSBB patients (normal and non-normal distribution)

Indicator	NSBB (n = 97) M ± SD	No EVL (n = 91) M ± SD	Statistical significance
Normal distribution (M ± SD)			
Age	49.78 ± 12.19	46.41 ± 12.89	NS
Hemoglobin (g/L)	117.45 ± 24.11	114.59 ± 24.87	NS
White blood cells ($\times 10^9$/L)	3.21 ± 0.81	3.24 ± 0.75	NS
Platelets ($\times 10^9$/L)	78.57 ± 34.91	72.45 ± 36.89	NS
Serum albumin (g/L)	35.19 ± 4.84	32.81 ± 4.92	NS
MELD-Na	22.01 ± 4.35	20.35 ± 5.67	NS
Non-normal distribution (Me; IQR)			
INR	2.01 (1.57–2.52)	1.99 (1.64–2.47)	NS
Bilirubin (μmol/L)	71.5 (58.00–92.1)	68.1 (52.24–89.03)	NS
Creatinine (μmol/L)	91.2 (64.51–123.1)	89.6 (60.8–122.5)	NS
Na (mmol/L)	132.7 (117.1–154.0)	137.7 (103.9–176.1)	NS

Note: NS, no statistically significant difference ($p > 0.05$) between the compared parameters.

As can be seen from the data presented in these tables, the compared patient groups did not differ in terms of demographics, clinical, laboratory parameters, or structure of etiology of cirrhosis. There were no significant differences when comparing MELD-Na scores and the incidence of grade B and C in determining liver severity by CTP. Patients in both groups did not differ in terms of incidence of grade 2 and grade 3 ascites. Comparable groups had no statistically significant differences in the incidence of medium-sized (second degree) and large-sized (third degree) esophageal varices.

Thus, prior to therapy, the compared groups were comparable in terms of demographic, clinical, and laboratory parameters, etiology of cirrhosis, severity of liver lesions, severity of ascites, and incidence of medium- and large-sized esophageal nodules.

While waiting for liver transplantation for 1.5 months to 36 months, 138 patients in the compared groups developed variceal bleeding. In the group of patients treated with NSBBs during this period, bleeding esophageal varices developed in 51 patients, while in the non-NSBB group, bleeding developed in 87 patients (52.6% and 95.6%, respectively, p = 0.0001). These differences when comparing the NSBB and non-NSBB groups are demonstrated by a comparative analysis of the percentage of non-bleeding patients obtained using the Kaplan–Meier estimate with the definition of the log-rank test (p = 0.0001) (Fig. 1).

Table 2

Comparative characteristics of parameters of NSBB and non-NSBB patients

Indicator	NSBB (n = 97) (%)	No NSBB (n = 91) (%)	Statistical significance
Male	57 (58.8%)	52 (57.1%)	NS
Virus-induced cirrhosis	57 (58.8%)	53 (58.2%)	NS
Alcohol-induced cirrhosis	40 (41.2%)	38 (41.8%)	NS
Ascites, grade 2	67 (69.1%)	65 (71.4%)	NS
Ascites, grade 3	30 (30.9%)	26 (28.6%)	NS
Varicose veins, grade 2	62 (68.1%)	63 (69.2%)	NS
Varicose veins, grade 3	35 (31.9%)	28 (30.8%)	NS
CTP, class B	7 (7.2%)	8 (8.8%)	NS
CTP, class C	90 (92.8%)	83 (91.2%)	NS

Note: NS, no statistically significant difference (p > 0.05) between the compared parameters.

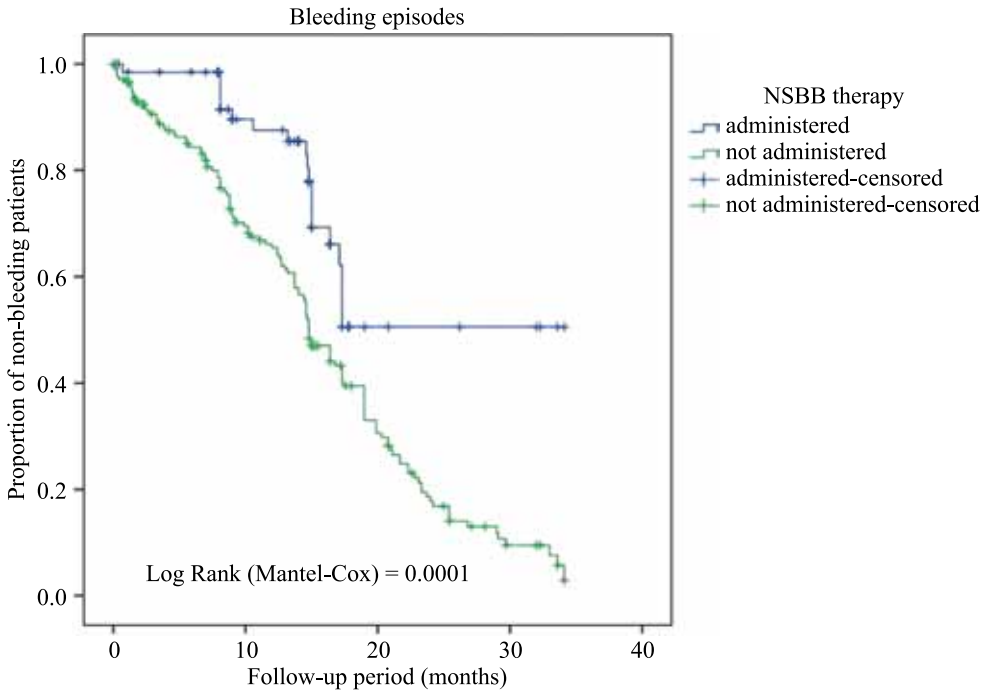

Fig. 1. Proportion of non-bleeding patients with and without NSBB therapy (Kaplan–Meier estimate with Log-Rank test). NSBB, non-selective beta-blockers; Log-Rank (Mantel–Cox) test, log rank nonparametric test for comparing survival curves, p = 0.0001

During this LTx waiting period, 145 patients died (58 from the NSBB and 87 from the non-NSBB group). Patient survival (Fig. 2) was significantly higher in the NSBB group than in the non-NSBB group (40.2% and 4.4%, respectively, p = 0.0001).

DISCUSSION

The progressive course of cirrhosis, characterized by a transition from a compensated to a decompensated form, manifested by the development of ascites, varicose vein bleeding and gastric variceal bleeding, is associated with an inordinately high increase in mortality [14]. In our study, we met patient selection criteria for primary prophylaxis of bleeding in patients with decompensated cirrhosis, ascites and non-bleeding varicose veins. In particular, the consensus on treatment of CSPH and its complications recommends primary prevention of bleeding in order to reduce the likelihood of further cirrhosis decompensation and mortality in patients with ascites and medium- and large-sized varicose veins [1, 11].

Unfortunately, in some patients, this therapy was not possible due to contraindications or intolerance of the drugs. It is known that some patients with cirrhosis have absolute or relative contraindications to traditional NSBBs, in particular those with peripheral vascular diseases, diabetes mellitus, chronic obstructive pulmonary disease, and bronchial asthma [15]. In this case, EVL is recommended in patients with ascites and CSPH to prevent bleeding and further decompensation of cirrhosis [1, 11]. In our study, a part of patients refused to use this intervention, which was the reason for them being included in the comparison group.

In our study, bleeding incidence was significantly lower in patients with ascites who received NSBBs as primary prophylaxis of bleeding than in the group of patients who did not receive this intervention. It should be emphasized that patients with ascites represent a group of patients at very high risk of variceal bleeding, and other life-threatening complications of cirrhosis, as they have a high hepatic venous pressure gradient (HVPG) [16].

It has been found that NSBBs are not effective in all patients with ascites. For example, of 452 patients with ascites, only 188 cirrhotic patients (42%) responded to NSBBs (a >20% decrease from baseline), resulting in lower odds of bleeding varicose veins, refractory ascites, spontaneous bacterial peritonitis, or hepatorenal syndrome [17]. In another study, Paternostro et al. [18] reported that HVPG-response to NSBBs within 90 days was achieved in 55.3% with cirrhosis and varices. The authors emphasized that absolutely all bleeding events occurred in HVPG-NSBB non-responders.

How can one identify among patients who will potentially respond to NSBB therapy and those who will not? The gold standard for monitoring hemodynamic response to NSBB therapy and investigating the severity of portal hypertension is the invasive method for determining HVPG [11, 19]. Decrease in HVPG level below 12 mm Hg or by 10% during primary prophylaxis of bleeding indicates **chronic** hemodynamic response to oral NSBBs [20]. However, determining this response requires repeated (second) invasive measurement of

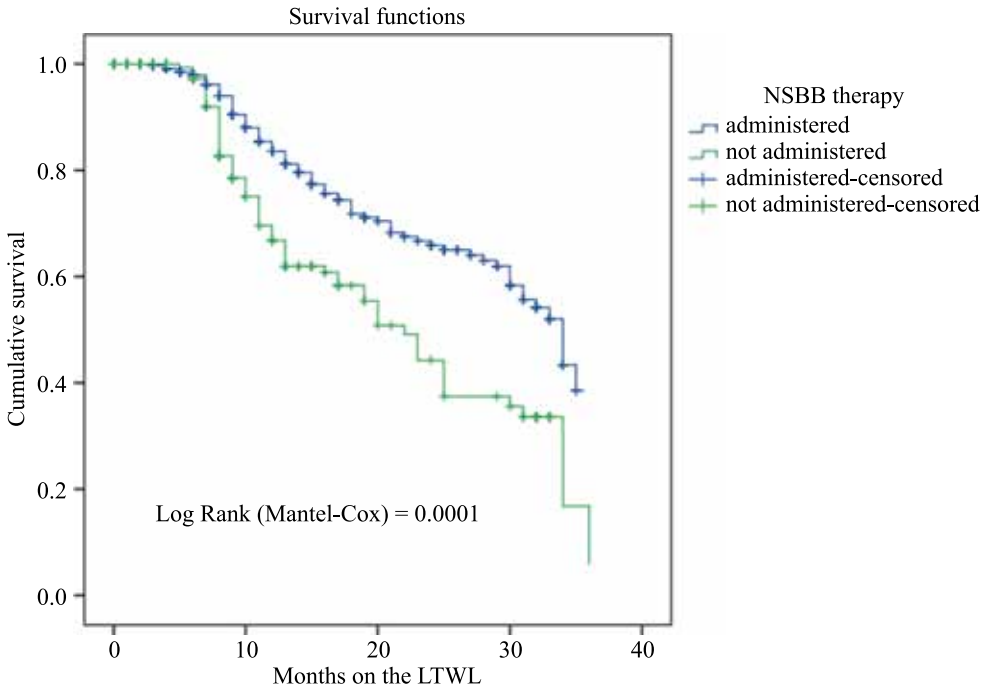

Fig. 2. Survival of patients in the NSBB and non-NSBB groups (Kaplan–Meier estimate with Log-Rank test). NSBB, nonselective beta-blockers; Log-Rank (Mantel–Cox) test, log rank nonparametric test for comparing survival curves, p = 0.0001

HVPG, and in some cases, between the first and second measurements, patients develop varicose vein bleeding, making it difficult to assess the chronic hemodynamic response to NSBBs [21]. An alternative to the first method has been proposed – to study of **acute hemodynamic response** to intravenous propranolol (≥10% reduction in HVPG levels) that helps to eliminate the disadvantages of the first method, potentially predicting the development of **chronic hemodynamic response** to oral NSBBs [22, 23].

So, the study of acute hemodynamic response to intravenous propranolol allows to stratify the risk of bleeding varicose veins at the early stage of portal hypertension during a single invasive study, reducing the need for repeated HVPG measurements [22, 23]. It has been found that acute hemodynamic response to propranolol during primary prevention of varicose vein bleeding actually reduces not only the development of the first bleeding, but also reduces the progression of ascites to more severe forms, development of ascites refractory to diuretics, reduces the development of spontaneous bacterial peritonitis and hepatorenal syndrome [20, 22].

Hofer et al. [24] found that acute hemodynamic effect on intravenous propranolol in patients with cirrhosis and CSPH is associated with a significant reduction in the risk of bleeding and hepatic decompensation. The authors confirmed different categories of patients when evaluating their response to NSBB therapy. In patients with decompensated cirrhosis, acute hemodynamic response on propranolol (58.2% of patients) were associated with a reduced risk of variceal bleeding at 12 months follow-up (3.6% responder; 15% nonresponder, log-rank, $p = 0.038$).

The disadvantages of our study include the limited technical capabilities of the center in determining HVPG, and, consequently, the absence of the possibility of acute or chronic hemodynamic response to NSBBs. In this regard, we can assume that significant development of bleeding in the NSBB group in our study is related to the presence of a category of HVPG-NSBB non-responders.

We found that the survival rate of patients with ascites who received NSBBs while waiting for LTx was significantly higher than the survival rate of cirrhotic patients whose therapy did not include NSBBs.

The effect of NSBBs on the survival of patients with decompensated cirrhosis is mixed. Conclusions by authors who have studied this problem vary, and, at times, contradict directly. For example, Sersté et al. [25] found that the 1-year survival of patients with refractory ascites decreased in the group of patients receiving propranolol. Kalambokis et al. [26] conducted a retrospective study of patients with cirrhosis of mixed etiology (96 CTP B and 75 CTP C), including alcoholic, viral and other etiologies, who had not previously received NSBBs. There were no significant differences in both groups (NSBB and non-NSBB) when comparing by gender, etiology of cirrhosis, and MELD score. Compared with those who did not receive NSBBs therapy, there was a significantly higher increase in 2-year mortality in the group with CTP B receiving this therapy. In the short-term follow-up (up to 6 months), there was a significant increase in mortality in the NSBB group than in the non-NSBB group among patients with CTP C or a MELD score of 16. Calès et al. [27] investigated the effect of NSBBs on liver-related mortality in a study of patients with alcohol-induced cirrhosis for over 5 years of follow-up. The authors found that the use of NSBBs (propranolol) reduced survival in patients with alcohol-induced cirrhosis associated with liver disease (MELD ≥12) compared with patients who did not receive these drugs. At the same time, NSBBs increased non-liver survival compared with patients without NSBB therapy.

A number of scientific publications have failed to note the effect of NSBBs on patient survival [28–30]. For example, Snoga et al. [30] stratified patients into those receiving and not receiving NSBBs therapy with the study of 24-month mortality in both groups of patients. The NSBB group and the non-NSBB group had similar patient mortality at 24 months (32.0% and 38.5%, respectively, $p = 0.51$). There were no significant differences in the proportion of bleeding and the proportion of patients who died from CSPH progression. In multivariate logistic regression, NSBB therapy was not a predictor of 24-month mortality.

A significant number of studies have found improved patient survival when comparing groups of cirrhotic patients receiving and not receiving NSBB therapy [31–33]. For instance, Ngwa et al. [31] investigated NSBB impact on the survival of patients enrolled in LTWL. NSBB use was associated with lower 90-day mortality (6% vs. 15%, $p = 0.03$). Patients taking NSBBs developed acute kidney injury (AKI) within 90 days more frequently (double) than patients not taking NSBB (22% vs 11%, $p = 0.048$). Twenty-seven percent of patients with >90 day follow up discontinued NSBB, most commonly for hypotension and AKI, had increased subsequent MELD and mortality. Sharma et al. [32] showed that survival of patients with large-sized varicose veins with primary prophylaxis of bleeding using NSBBs increased.

CONCLUSION

NSBBs constitute an efficacious therapy in the primary prophylaxis of variceal bleeding, thereby saving life and preventing attrition of patients with ascites from the liver transplant waitlist. The introduction of patient selection techniques for NSBBs by means of acute hemodynamic response testing on propranolol when measuring HVPG is a promising measure that significantly improves prognostic response in primary prophylaxis of bleeding.

The authors declare no conflict of interest.

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