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USE OF ENDOSCOPIC BAND LIGATION ALONE AND IN COMBINATION WITH NONSELECTIVE BETA BLOCKERS FOR PREVENTION OF VARICEAL BLEEDING IN ASCITES PATIENTS ON THE LIVER TRANSPLANT WAITING LIST

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Objective: to conduct a comparative analysis of the effectiveness of two methods – endoscopic band ligation (EBL) alone and in combination with nonselective beta blockers (NSBB) – used for prevention of variceal bleeding (VB); to evaluate their impact on patient survival in severe ascites during long-term stay on the liver transplant waiting list (LTWL). **Materials and methods.** A retrospective comparative study of two groups of patients with decompensated liver disease, ascites and varices included in the LTWL, who received EBL (n = 41, group 1) and EBL + NSBB (n = 45, group 2). **Results.** The groups being compared did not differ in demographics, clinical parameters, MELD and Child–Turcotte–Pugh scores. There were no significant differences in the incidence of severe ascites, particularly diuretic-resistant ascites. The study groups did not differ in the incidence of medium- and large-sized varices. Incidence of bleeding did not differ in both groups. Overall mortality was significantly higher in the EBL + NSBB group than in the EBL group. Patient survival was lower, while mortality was higher in the EBL + NSBB group. The combined therapy group had a significantly higher number of acute kidney injury (AKI) than the EBL group. **Conclusion.** The compared methods are equivalently effective in preventing VB in patients with decompensated cirrhosis with a prolonged stay on the waiting list. Survival rate is significantly lower, while mortality is significantly higher in the EBL + NSBB group than in the EBL group.

Keywords: liver transplant waiting list, ascites, bleeding, nonselective beta blockers, endoscopic band ligation.

INTRODUCTION

The introduction of various types of liver transplantation (LTx) into clinical practice has made irreversible liver diseases highly curable. LTx has become the therapy of choice for end-stage liver diseases, acute liver failure and selected cases of hepatocellular carcinoma (HCC) [1]. Decompensated cirrhosis is one of the main indications for LTx [2, 3]. Increase in the number of liver transplantations due to expanded indications, as well as a significant increase in potential recipients on the liver transplant waiting list (LTWL), which have been witnessed worldwide in recent years, have led to an acute problem of organ (liver) shortage in almost all countries of the world [4]. Acute shortage of liver donors has raised the challenge of preserving life and preventing dropout of patients from the LTWL. Portal hypertension (PH) is a major complication of cirrhosis, characterized by increased pressure in the portal venous system, leading to portosystemic collateral vasculature [5, 6]. Dilated veins of the esophagus and stomach constitute a real clinical problem due to their possible rupture with subsequent catastrophic bleeding [5], which is the main cause of death in patients with cirrhosis, including those waiting for LTx [7]. The prevalence of esophageal varices (EV) varies between 40% and 95% in patients with cirrhosis [8, 9]. The annual detection rate of EV in patients with clinically significant portal hypertension (CSPH) varies from 3% to 22% [10–12]. Approximately 15–20% of patients with cirrhosis develop bleeding within 1 to 3 years [13, 14]. In short-term follow-up, the mortality rate in the event of a VB episode varies from 15% to 30% [15–18].

The 5-year VB-associated mortality in patients with cirrhosis is over 80% [19]. Mortality due to VB is usually determined by size of varices or basal liver function [20]. According to the Baveno VI guideline, 2 major axes of primary prophylaxis for varices are suggested: NSBB and EBL [21]. EBL is a physical method that rarely causes hemodynamic changes. On the contrary, NSBB can induce hemodynamic changes by reducing cardiac output (CO) and vasodilation [22]. In this context, it is unclear whether the use of NSBB is actually beneficial for end-stage liver disease [21, 23].

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Serste et al. [22] first showed the risk of NSBB use in this category of patients and proposed the "therapeutic window" hypothesis for NSBB use, considering the optimal use of this class of drugs in cirrhosis progression [20]. These researchers concluded that NSBB should be used with caution in decompensated cirrhosis. Among the unresolved problems that would confirm their usefulness is the use of NSBB in decompensated liver or in refractory ascites (RA).

Ascites is one of the most common complications of cirrhosis. In the practice of physicians managing patients in the LTWL, cases of simultaneous development of ascites and VB is not uncommon. In patients with different etiologies of cirrhosis, CSPH is the main driver of complications such as ascites or VB [23]. It is unknown whether NSBB is useful or, on the contrary, dangerous for patients with ascites and VB.

An important aspect of this problem is that in most works containing optimistic results, the effectiveness of NSBB was evaluated in the short term, on average about 6 months [24, 25]. Taking into account the fact that the average patient survival in VB is about 2 years, it is very difficult to interpret the above results with a positive outcome of NSBB in the short-term management period on a population of LTWL patients for 2 years or more.

In this regard, the **objective** of this work was to compare the effectiveness of two methods (EBL alone and EBL plus NSBB) used for prevention of VB so that their impact on the survival of patients with severe ascites during long-term stay in the LTWL could be evaluated.

MATERIALS AND METHODS

The study was conducted at the Center for Surgery and Donor Coordination, Rostov Regional Clinical Hospital. It was approved by the local ethics committee. The analysis included data from 86 waitlisted patients with cirrhosis of various etiologies (viral, alcoholic). EV was detected via screening endoscopy, which led to us preventing bleeding in 45 patients by prescribing NSBB (carvedilol, propranolol, nadolol) in combination with EBL; in 41 patients, EBL was used without subsequent prescription of NSBB. Patient demographic and clinical data were obtained from a continuously updated electronic database.

Inclusion criteria: presence of EV, grade 2 or 3 ascites by the time of initiation of VB prophylaxis.

Exclusion criteria: patients with HCC or other malignancies with the development of ascites, patients who have used NSBB for <4 weeks, patients who have undergone LTx, patients with heart rate <60/min and/or systolic blood pressure (SBP) <90 mmHg.

MELD-Na [26] and Child–Turcotte–Pugh [27, 28] scores were calculated. Ascites severity was determined in accordance with the International Ascites Club guidelines [29]. During screening endoscopy, EV with high risk of bleeding were determined and named "varices needing treatment" ("VNT") according to Baveno VI [21] and World Gastroenterology Organisation (WGO) criteria [30] in the foreign literature. Advanced diagnostic criteria of the International Ascites Club were used to diagnose AKI in cirrhosis [31].

In waitlisted patients with alcoholic cirrhosis, abstinence confirmed by narcologists and psychiatrists was maintained for at least 3 months. Patients with cirrhosis associated with HBV and HCV infections received antiviral therapy with nucleoside analogues and a combination of direct-acting antivirals, respectively. All patients in the LTWL underwent clinical and biochemical investigations; their hemostasis parameters were examined. When the patients were stable, blood tests were repeated at 3-month intervals, ultrasound examinations were repeated at 6-month intervals.

The primary endpoint of the study was to evaluate patient survival in the compared groups: those receiving EBL and those receiving EBL plus NSBB.

NSBB was administered under control of heart rate and blood pressure, adjusting the dose when these parameters decreased. The initiating propranolol dose was 40 mg/day, the maximum dose was 240 mg/day. Carvedilol was started with 6.25 mg/day initiating dose, the maximum dose was 25 mg/day. Nadolol was started at 40 mg/day, with a maximum dose of 80 mg/day.

EBL was performed under sedation via esophagogastroduodenoscopy and band ligation of EV. Each EV was ligated with one or two latex ligatures (rings). Esophageal variceal ligation began at the gastroesophageal junction and continued proximally. As a rule, EV ligation was performed with 2 to 4 rubber ligatures or more, depending on the size of the EV. All patients underwent repeated procedures 4 weeks later until all EV meeting the WNT criteria [21] were obliterated. After EV obliteration, control esophagogastroduodenoscopy was performed at 3-month intervals. If a recurrence developed (a new EV appeared), repeated ligation procedures were performed.

All patients received diuretics, in some patients, in case of development of resistance to therapy, paracentesis was performed.

Statistical analysis of the data was carried out using the IBM SPSS Statistics program version 23. The Kolomogorov–Smirnov test was used to check the normal distribution of the indicators obtained during the study. Sample data with a normal distribution of the received data were presented as arithmetic means (M) and standard deviation (SD, standard deviation) with a 95% confidence interval (CI) determined. The statistical significance of differences between the compared values in the case of a normal distribution was determined by Student's t-test. In the absence of a normal distribution of obtained values of the studied indicators, the following nonparametric tests were used: Wilcoxon for paired comparisons of dependent variables, Mann–Whitney U-test,

Pearson's chi-squared test – for comparisons of independent variables. Quantitative indicators in samples with non-normal distributions were expressed as median and interquartile range (IQR, the interval between the 25th and 75th percentiles). For qualitative data, frequencies and fractions (%) were calculated. Differences between compared parameters were considered statistically significant if the probability of error was less than 0.05 ($p < 0.05$). Patient survival in the compared groups (EBL and EBL + NSBB) was determined by the Kaplan–Meier estimate; the log-rank (Mantel-Cox) test was used to compare survival. Predictors of waitlist mortality in the compared groups was also performed using the Cox proportional-hazards model with calculation of the hazard ratio (HR).

RESULTS

The mean waitlist follow-up was 46.8 months with ICR (1.4–65.2 months). A total of 86 patients with a mean age of 48.6 ± 13.1 years were included in the study, including 68 men (80%) and 18 women (20%). Table 1 and Table 2 present demographic, clinical, laboratory, and index data (MELD-Na, Child–Turcotte–Pugh) in the groups of patients with ascites who underwent EBL (n = 41) and EBL + NSBB (n = 45) for VB prevention during their stay in the LTWL. Of the 86 patients, 21 (24.4%) had no VB before being waitlisted, and 65 (75.6%) patients had VB before inclusion in the liver transplant waiting list.

There were no statistically significant differences in the structure of cirrhosis etiology (viral, non-viral). In both groups, patients had severe liver dysfunction as assessed by MELD index and Child–Turcotte–Pugh class of cirrhosis without significant differences between the compared groups. Grade 2 ascites predominated in both groups without statistically significant differences between the groups; the proportion of grade 3 ascites was also comparable in the compared groups (19.5% and 17.8%, respectively, $p > 0.05$). Of the 86 patients, the vast majority were on diuretics (83 patients, 96.5%). In the EBL group, 40 patients (97.6%) took diuretics; in the EBL + NSBB group, 43 patients (95.6%) did. There were no significant differences in the frequency of diuretics between the compared groups ($p < 0.05$). Intermittent paracentesis was performed against the background of diuretics in diuretic-resistant patients. There were no significant differences in RA incidence in the compared groups (14.6% and 17.7%, respectively, $p > 0.05$).

Table 1

Comparative characteristics of parameters of EBL and EBL + NSBB patients (normal distribution)

Indicator	EBL (n = 41) M ± SD	EBL + NSBB (n = 45) M ± SD	Significance of difference
Age	47.49 ± 11.16	49.59 ± 12.35	NS
Hemoglobin, g/L	113.43 ± 23.38	112.55 ± 25.61	NS
White blood cells $\times 10^9$/L	3.12 ± 0.43	3.07 ± 0.76	NS
Platelets, $\times 10^9$/L	98.39 ± 31.43	102.12 ± 35.43	NS
Plasma albumin, g/L	36.23 ± 4.54	34.74 ± 7.42	NS
MELD-Na	24.43 ± 4.35	25.45 ± 8.44	NS

Note: NS (non-significant), no statistically significant difference ($p > 0.05$) between compared values.

Table 2

Comparative characteristics of parameters of EBL and EBL + NSBB patients (no normal distribution)

Indicator	EBL (n = 41) Median (IQR) or [%]	EBL + NSBB (n = 45) Median (IQR) or [%]	Significance of difference
Male	32 (78.05%)	36 (80%)	NS
Viral etiology of cirrhosis	17 (41.5%)	21 (46.7%)	NS
Nonviral etiology of cirrhosis	24 (58.5%)	24 (53.3%)	NS
Ascites, grade 2	33 (80.5%)	37 (82.2%)	NS
Ascites, grade 3	8 (19.5%)	8 (17.8%)	NS
Varices, grade 2 (VNT)	21 (51.2%)	24 (53.3%)	NS
Varices, grade 3 (VNT)	20 (48.8%)	21 (46.7%)	NS
Child–Turcotte–Pugh, class B	23 (56.1%)	25 (55.6%)	NS
Child–Turcotte–Pugh, class C	18 (43.9%)	20 (44.4%)	NS
INR	2.05 (1.625–2.775)	1.95 (1.7–2.05)	NS
Creatinine, μmol/L	142.0 (110.0–198.25)	148.0 (111.5–202.5)	NS
Bilirubin, μmol/L	91.0 (67.25–206.5)	89.0 (62.5–987.5)	NS
Na, mmol/L	139.5 (138.0–141.0)	137.5 (135.5–143.5)	NS

Note: NS (non-significant), no statistically significant difference between compared values.

The compared groups had no statistically significant differences in the incidence of EV classified as VNT (NS).

No significant differences were found in the compared groups (NS) in terms of demographic, laboratory parameters.

During the stay in the LTWL, 39 patients died – 11 in the EBL group and 28 in the EBL + NSBB group. Table 3 shows the overall mortality, VB-associated mortality, liver dysfunction-associated mortality, and mortality due to other causes, as well as clinical outcomes (complications) developed during the therapy in the compared groups. As shown in Table 3, overall mortality was significantly higher in the EBL + NSBB group than in the EBL group. The VB-associated mortality, as well as liver dysfunction-associated mortality had no significant differences between the compared groups. At the same time, mortality associated with causes other than variceal bleeding or liver failure – portal vein thrombosis and renal dysfunction – was significantly higher in the group of patients receiving combined therapy than in the group of patients treated with EBL alone. There were no significant differences in the incidence of bleeding and spontaneous bacterial peritonitis against the background of the therapy in both compared groups. AKI developed more frequently in the group of patients treated with combination therapy (EBL + NSBB) than in the group treated with EBL alone.

Patient survival as determined by the Kaplan–Meier estimate (Fig. 1) was significantly higher in the EBL-treated group than in the EBL + NSBB group (log-rank = 0.001). The risk of death (Fig. 2) was significantly higher in the combination therapy (EBL + NSBB) group than in the EBL group (HR = 5.139; p = 0.005).

DISCUSSION

Cirrhosis is known to be the final stage attained by chronic liver diseases and it is the main cause of patient death regardless of its etiology. To date, two quite distinct stages of cirrhosis have been clearly formulated: compensation and decompensation, with different prognosis and pathophysiological mechanisms [32]. Compensated cirrhosis is a long-term asymptomatic stage, with average patient survival of over 12 years, while decompensated cirrhosis, whose main pathophysiological driver is CSPH, leads to VB, ascites, hepatic encephalopathy with a sharp decrease in patient survival – less than 2 years [23, 32].

Our study included patients with decompensated cirrhosis with the presence of ascites, risk of bleeding or VB.

It is known that ascites progression and bleeding are the leading causes of death in LTWL patients [7]. According to the updated Baveno VI guidelines, prevention of progression of decompensated cirrhosis and development of the first bleeding includes use of NSBB or EBL (primary prophylaxis) in patients with ascites, large varices (VNT), or with Child–Turcotte–Pugh classification class C. In order to prevent recurrent VB (secon-

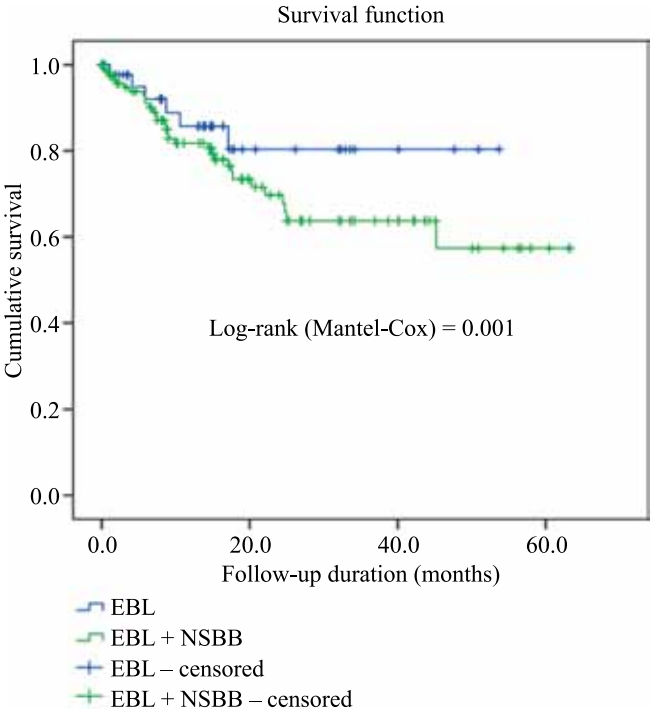

Fig. 1. Patient survival using Kaplan–Meier method with log-rank (Mantel-Cox) test in the EBL and EBL + NSBB groups

Table 3

Comparison of mortality and other clinical outcomes in EBL and EBL + NSBB patients

Indicator	EBL (n = 41) [%]	EBL + NSBB (n = 45) [%]	Significance of difference
Overall mortality	11 (26.8%)	16 (62.2%)	p = 0.001
Mortality associated with bleeding	3 (27.3%)	4 (25.0%)	NS
Mortality associated with liver failure	7 (63.6%)	9 (56.25%)	NS
Mortality associated with other causes	1 (9.1%)	3 (18.75%)	p = 0.002
Variceal bleeding	8 (19.5%)	10 (22.2%)	NS
Spontaneous bacterial peritonitis	2 (4.9 %)	3 (6.7%)	NS
Acute kidney injury	4 (9.75%)	9 (20%)	p = 0.031

Note: NS (non-significant), no statistically significant difference between compared values.

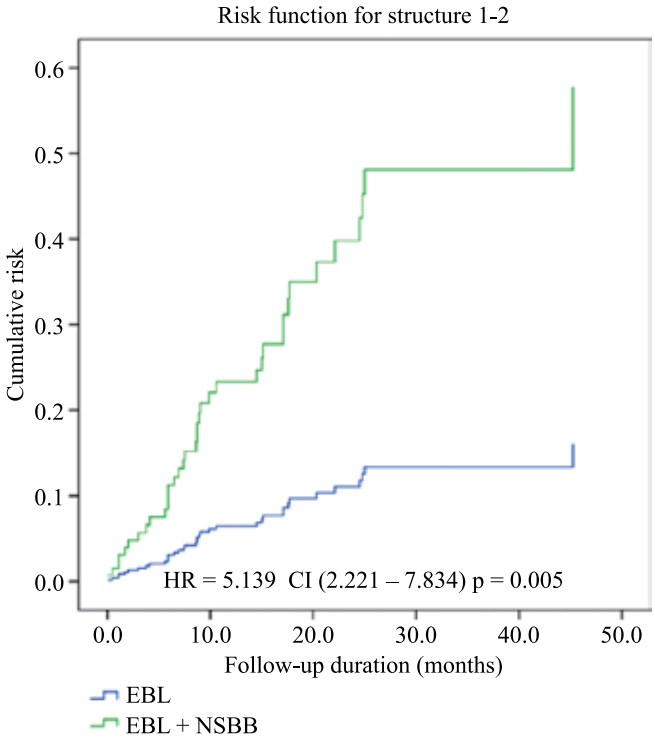

Fig. 2. Mortality in EBL and EBL + NSBB groups. Cox proportional hazards model with calculation of the Hazard Ratio (HR)

dary prevention), this consensus recommends the use of first-line therapy (combination of NSBB and EBL) [33].

In accordance with these guidelines, we used the NSBB + EBL combination predominantly for secondary prevention of variceal bleeding, and EBL for primary prevention. Although Baveno VI does not recommend the NSBB + EBL combination for primary prevention of VB, and EBL as an independent method of secondary bleeding prevention, these strategies are used in clinical practice [34]. In this regard, EBL procedure was used in a part of patients (about 30%) with a history of bleeding before inclusion in the LTWL, while the NSBB + EBL combined therapy was used in patients with no bleeding (35%).

Our analysis showed that both methods effectively prevented bleeding, achieving the objectives of primary and secondary prevention, as evidenced by the low incidence of VB and associated patient mortality against the background of the therapy; and there were no significant differences in bleeding incidence in the compared patient groups.

Nevertheless, we noted significant differences when assessing the overall patient mortality and survival in the compared groups. Overall mortality was significantly higher and patient survival was significantly lower in the EBL + NSBB group than in the EBL group. Similar results were obtained when analyzing mortality associated with the development of portal vein thrombosis and AKI. The EBL + NSBB patients were significantly more likely to develop AKI than their EBL counterparts.

How can these discouraging results in our research be explained? Indeed, propranolol, nadolol, and carvedilol have been shown to be useful agents in randomized clinical trials when used in patients with ascites and VNT, being a first-line therapy in the prevention of VB [33, 35]. However, in the above studies, patients with severe and, especially, refractory ascites, who are highly likely to develop AKI, were excluded from calculations [36]. Accordingly, even the updated guidelines for management of patients with ascites and the risk of VB [33, 36] cannot be automatically extrapolated to patients with severe decompensated cirrhosis with significant hemodynamic disorders [37, 38]. This is probably confirmed by our data indicating an increase in mortality in patients with ascites who received combined therapy (EBL + NSBB), as well as an increase in patients with AKI in the same group of patients. Undoubtedly, decreased patient survival and increased risk of mortality obtained for this patient cohort are also associated with the adverse effects of NSBB on hemodynamics.

Three pathophysiological mechanisms may explain the negative impact of NSBB on ascites patients at high risk for VB. First, in at least some patients with ascites, the cause of high mortality is a decrease in mean arterial pressure (SBP, MAP in the English literature). MAP develops during all phases of the cardiac cycle, is the product of CO and total peripheral resistance (OPS), to which is added the value of the central venous pressure (CVP). It has been shown that in a large cohort of waitlisted patients with ascites, NSBB significantly reduced patient survival due to a decrease in MAP <80 mm Hg [39]. Secondly, NSBB, by inhibiting the increase in compensatory CO in response to increased vasodilation, leads to a significant decrease in the survival of patients with cirrhosis and RA [40]. Thirdly, NSBB through β-adrenergic receptor blockade is associated with higher risk of kidney damage (AKI and hepatorenal syndrome (HRS)) in patients with severe decompensated cirrhosis (Child–Turcotte–Pugh class C). Thus, the risk of developing HRS and AKI was three times higher in patients with ascites who received NSBB compared to patients who did not receive these drugs [41]. In cirrhosis patients with ascites, who are included in the LTWL, the risk of developing post-NSBB AKI was increased by more than three times compared with patients without ascites, in whom the use of these drugs was associated with an 80% reduction in AKI incidence [42].

It should be noted that a number of foreign researchers have shown results similar to ours. For example, Jeong-Ju Yoo et al. [43] found a significant decrease in survival and an increase in overall mortality in patients who received combined propranolol and EBL therapy compared to patients who received EBL only.

CONCLUSION

Our studies have shown that both methods (EBL and EBL + NSBB) performed for primary or secondary prevention of VB, effectively reduce VB incidence. However, the presence of ascites, and especially RA, significantly increases mortality in patients treated with the EBL + NSBB combination. Reduced patient survival in this group is probably due to the negative impact of NSBB on cardiovascular haemodynamics at this stage of PH progression (reduced SBP, reduced CO), which in turn results in reduced renal perfusion and a significant increase in AKI. In order to improve patient survival, it is necessary to differentiate the use of different representatives of this class depending on the cardiac hemodynamics parameters and to apply the NSBB dose titration principle.

The authors declare no conflict of interest.

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