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AZYGOPORTAL DISCONNECTION OR A COMBINATION OF NON-SELECTIVE BETA-BLOCKERS AND ENDOSCOPIC VARICEAL LIGATION TO PREVENT RECURRENT BLEEDING IN PATIENTS WITH CIRRHOSIS AWAITING TRANSPLANTATION

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Objective: to compare the efficacy of azygoportal disconnection (APD) surgery and a combination between endoscopic variceal ligation (EVL) and non-selective beta-blockers (NSBBs) in the prevention of recurrent variceal bleeding (RVB). To compare the incidence of gastric variceal bleeding (GVB) after these manipulations in patients with decompensated cirrhosis waitlisted for liver transplantation (LTx). **Materials and methods.** Patients with decompensated cirrhosis underwent RVB prophylaxis by APD surgery or by a combination of EVL and NSBBs. **Results.** There were no significant differences in clinical, laboratory, demographic parameters, MELD-Na and Child–Turcotte–Pugh (CTP) scores, and frequencies of medium- and large-sized varicose veins among subgroups of patients with different RVB prophylaxis methods Patients with decompensated cirrhosis who underwent APD surgery did not experience any RVB episodes during the LTx waiting period, which lasted two years from the start of bleeding prophylaxis. In the same period, RVB occurred in 100% of cases in the EVL plus NSBBs group. Using the Kaplan–Meier method with the Log-Rank test, a significant difference ($p = 0.0001$) was found between the proportions of non-RVB patients in the APD and EVL + NSBBs groups. In the meantime, 48.1% of patients who had APD surgery developed GVB, while 100% of cases in EVL + NSBBs group did not. The Kaplan–Meier method with the Log-Rank test revealed a significant difference ($p = 0.0001$) between the proportion of non-GVB patients in EVL + NSBBs and APD groups.

Keywords: liver transplant waiting list, recurrent variceal bleeding, gastric variceal bleeding, endoscopic variceal ligation, nonselective beta-blockers, azygoportal disconnection.

INTRODUCTION

The transition from compensated to decompensated cirrhosis, which is an indication for inclusion in the waiting list for liver transplantation (LTx) [1], is accompanied by clinically significant portal hypertension (CSPH), in which the leading cause of mortality among patients waiting for LTx is bleeding varicose veins [1–3]. It is known that after the first episode of bleeding esophageal varices, there is a high probability of recurrent variceal bleeding (RVB) within 2–3 days after the patient's condition has stabilized, reaching a frequency of up to 60% within a week, if no measures are taken to prevent this CSPH complication [4, 5]. It was found that secondary prophylaxis of RVB in this patient cohort does not eliminate the risk of development in 60% of patients within 1 year [6] and in 29–57% within two years after the first bleeding episode [7].

Experts from Baveno VII recommend "first-line therapy" to prevent RVB. This involves endoscopic variceal ligation (EVL) in combination with traditional nonselective beta-blockers (NSBBs) or carvedilol [1]. If EVL is contraindicated or there is an intolerance to drug therapy, any of the components of this combination may be used. The expert council recommends implantation of a transjugular intrahepatic portosystemic shunt (TIPS) as a second-line therapy [1].

Even though TIPS implantation is effective in reducing CSPH levels by preventing RVB, its use is considered as a step towards subsequent LTx because of RVB caused by stent block [8] and subsequent development of portosystemic hepatic encephalopathy (HE) [9].

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Along with TIPS implantation, azygoportal disconnection (APD) surgery in various modifications has been proposed to prevent bleeding from the GDP [10, 11]. We have previously shown high efficacy of APD in the prevention of bleeding esophageal varices in patients awaiting LTx [12].

Objective: to compare the efficacy of APD surgery and a combination of EVL with NSBBs in the prevention of RVB. To compare the incidence of gastric variceal hemorrhage after these manipulations in patients with decompensated cirrhosis waitlisted for LTx.

MATERIALS AND METHODS

The comparative retrospective study included 177 patients with decompensated cirrhosis who were waiting for LT between 2016 and 2023 and had experienced at least one incident of bleeding varicose veins.

Inclusion criteria: patients with decompensated cirrhosis must have had at least one bleeding varicose vein during their stay on the liver transplant waitlist (LTWL); they must have had virus-related cirrhosis (HBV- or HCV-associated etiology), alcohol-related cirrhosis, or cirrhosis of mixed etiology (virus and alcohol); they must have completely abstained from alcohol for at least three months (confirmed by addiction specialists) prior to inclusion in the LTWL for patients with alcohol-related cirrhosis; they have Child–Turcotte–Pugh (CTP) classes B and C cirrhosis.

Exclusion criteria: hepatocellular cancer or other tumors, infectious diseases, portal vein thrombosis (PVT), contraindications to NSBBs (bradyarrhythmia, bronchial asthma, obstructive pulmonary disease), and diabetes mellitus.

The first group of patients included in the study consisted of 150 patients with a first bleeding episode who underwent EVL procedure in combination with NSBB administration. In cases where first-line therapy for prophylaxis of recurrent hemorrhage (endoscopic ligation in combination with non-selective beta-blockers) after stabilization of the patient's condition due to bleeding failed, 27 patients were routinely treated with APD.

All parameters included for subsequent analysis from a continuously updated electronic patient database (demographic, clinical and laboratory parameters) were obtained after approval of the study by the local ethics committee. Patient follow-up, including repeated studies of laboratory parameters, follow-up control of drug therapy, was carried out by specialists from the Center for Surgery and Donation Coordination, Rostov Regional Clinical Hospital.

When patients were enrolled in the LTWL, an examination was carried out on them, including laboratory and instrumental studies. These tests were repeated at 3-month intervals for stable patients (clinical and biochemical blood tests, haemostasis parameters, MELD-Na score and CTP score), and abdominal ultrasound was performed every 6 months. Whenever a patient's condition became unstable, laboratory and instrumental investigations were carried out as indicated.

In all patients, esophagogastroduodenoscopy (EGD) was performed to screen for varicose veins with high risk of bleeding (medium and large varicose veins) according to the Baveno VI Expert Committee [13] and World Gastroenterology Organisation (WGO) [14] guidelines.

The International Ascites Club (IAC) criteria were used to assess the severity of diuretic-responsive ascites [15]. The IAC criteria [15] and the CIRAS scale [16], which comprises clinical (no response to diuretic medication and increased volume of fluid in the abdominal cavity) and laboratory (plasma Na level <125 mmol/L) criteria, were used to diagnose diuretic-resistant ascites. For a score of 5–6 on this scale, diuretic-resistant ascites was considered well diagnosed [16].

Patients who responded to therapy received diuretics; patients with diuretic-resistant ascites underwent paracentesis.

After intravenous analgesia (sedation), EVL procedure was performed in a standard way using a varicose vein ligation kit and video esophagogastroduodenoscopy device. Varicose veins were ligated proximally, starting from the gastroesophageal junction. The number of rubber ligatures used varied from 2 to 4, depending on the size of the varicose veins. The EVL procedure was performed to obliterate all varicose veins fulfilling the criteria for emergency therapy [13, 14]. Repeated EGDs at 3-month intervals served as a control method, and if new varicose veins were found, the EVL procedure was repeated until the varicose veins were completely obliterated.

To perform APD surgery under total intravenous anesthesia, an upper midline laparotomy was carried out according to the standard technique. In order to adequately visualize the cardiac part of the stomach and the abdominal part of the esophagus, the gastroesophageal junction was lowered together with the fiber. The vagus nerve was isolated. Selective proximal vagotomy was performed. Mobilization of the stomach fundus and retroperitoneal part of the cardia with crossing of the vessels of the gastroesophageal ligament and branches of the left gastric artery and vein was performed. The abdominal part of the esophagus was isolated 6–8 cm above the lower esophageal sphincter with isolation, ligation and crossing of all collaterals, and then it was completely crossed at 2–3 cm from the esophageal-gastric recess. Using a linear stapler, we resected the part of the cardia facing the esophagus, 4–5 cm from the angle of His.

The second row of seromuscular sutures was used to reinforce the row of the machine stitch of the gastric stump. The stomach body was juxtaposed with the esophagus by moving its stump toward the liver. Next, a new ligamentous apparatus was formed by fixing the esophagus to the diaphragm legs with two ligamentous

sutures. The least vascularized zone was visually determined on the anterior wall of the stomach body, where a double-row esophagogastric anastomosis (EGA) was formed with a precision suture using PDS 5/0 monofilament. Then an anti-reflux cardia was formed: esophagus and EGA zone were wrapped with the stomach fundus, which was sutured and fixed with interrupted seromuscular sutures to the anterolateral surfaces of the esophagus and to the right and left diaphragm legs, closer to their thoracic part. Next, using single seromuscular sutures, the stomach fundus was fixed to the greater curvature and the anterior wall below the EGA, thus completing the formation of anti-reflux cardia.

The obtained data were analyzed using statistical software package IBM SPSS Statistics (version 23). Type of distribution of obtained variables of the studied samples was determined using the Kolmogorov–Smirnov test and the Lilliefors significance level. Where the variables are found to be of normal distribution, further analysis included calculation of arithmetic mean (M) and determination of standard deviation (SD). The significance of differences between compared variables was determined by Student's t test, using $p < 0.05$ as a criterion. The median (Me) with interquartile range (IQR, difference between the 25th and 75th percentiles) was used for further analysis of variables with non-normal distribution. The Wilcoxon test used for nonparametric analysis was used to determine the significance of differences in pairwise comparisons of dependent variables; Pearson's chi-squared test was used in comparisons of independent variables. The Mann–Whitney U test was used to compare variables in small sample sizes. ANOVA test was used for analysis of variance. Contingency tables were used in the analysis of qualitative parameters – frequencies of variables and their proportions (%); for small sample sizes, Fisher's exact test was used to assess the significance of the relationship between two variables.

The proportions of patients without RVB in the compared groups were determined by the Kaplan–Meier method. The significance of differences between the compared curves (patient proportions) was determined by calculating the log-rank test [Log-Rank (Mantel-Cox)].

RESULTS

Table 1 presents demographic, clinical, laboratory, and MELD-Na scores for the groups of patients who received NSBB therapy plus EVL or who underwent APD during the transplant waiting period.

Table 2 presents data on gender composition, as well as etiology of cirrhosis, CTP grade and severity of varicose veins in patients who received NSBB therapy plus EVL or who underwent APD surgery.

The compared groups (Table 1 and Table 2) were homogeneous in terms of demographic, clinical, and laboratory parameters, as well as in terms of MELD-Na scores, CTP classes B and C, and frequency of varicose veins of medium (grade 2) and large (grade 3) size.

All patients (100%) who underwent the EVL procedure in combination with receiving NSBBs developed RVB while waiting 2 years for LTx from the start of bleeding prophylaxis. Patients with decompensated cirrhosis who underwent APD surgery did not experience any RVB episodes during the LTx waiting period, which lasted two years from the beginning of bleeding prophylaxis.

Using the Kaplan–Meier method with the Log-Rank test, a significant difference ($p = 0.0001$) was found between the proportions of patients without RVB in the APD group and the NSBB + EVL group (Fig. 1).

Table 1

Comparative characteristics of EVL + NSBBs and APD patients (normal and non-normal distribution)

Indicator	EVL + NSBBs (n = 150) M ± SD	APD (n = 27) M ± SD	Statistical significance
Normal distribution (M ± SD)			
Age	49.76 ± 11.02	52.34 ± 10.89	p > 0.05
Hemoglobin (g/L)	89.96 ± 12.04	87.67 ± 11.99	p > 0.05
Leukocytes ($\times 10^9$/L)	3.46 ± 1.13	3.79 ± 1.75	p > 0.05
Platelets ($\times 10^9$/L)	89.35 ± 34.45	93.56 ± 42.23	p > 0.05
Plasma albumin (g/L)	31.12 ± 3.21	30.45 ± 2.89	p > 0.05
MELD-Na score	22.01 ± 3.11	21.92 ± 3.14	p > 0.05
Non-normal distribution (Me; IQR)			
INR	1.92 (1.65–2.10)	1.90 (1.62–2.12)	p > 0.05
Bilirubin (μmol/L)	86.5 (66.50–115.00)	84.0 (62.50–112.50)	p > 0.05
Creatinine (μmol/L)	110.2 (97.5–128.20)	109.4 (98.5–122.25)	p > 0.05
Na (mmol/L)	136.8 (132.0–140.5)	135.2 (128.5–142.5)	p > 0.05
CTP (points)	12.00 (8.00–14.50)	11.00 (8.50–14.00)	p > 0.05

Note: EVL, endoscopic variceal ligation; NSBBs, nonselective beta-blockers; APD, azygoportal disconnection; MELD-Na, Model for End-Stage Liver Disease-Sodium; INR, International normalized ratio; CTP, Child–Turcotte–Pugh; Na, sodium.

At the same time, bleeding from gastric varices occurred in 48.1% of APD patients, which was absent in 100% of EVL + NSBB patients. The Kaplan–Meier method with the Log-Rank test showed a significant difference ($p = 0.0001$) between the proportion of patients without bleeding gastric varices in the APD group or EVL + NSBB cohort (Fig. 2).

DISCUSSION

According to expert recommendations, secondary prophylaxis for RVB is performed through EVL in combination with traditional NSBBs or carvedilol (first-line therapy) [1]. Our study showed a high incidence of RVB in patients who waited for LTx for 24 months and were treated with secondary prophylaxis using first-line therapy (EVL + NSBBs). With this prophylaxis strategy, RVB started to develop from the first weeks of EVL in combination with NSBBs and continued up to 24 months (100% of cases). According to Garcia-Tsao et al. [6], the risk of developing RVB within a year is 60% despite bleeding prophylaxis.

It has been found that the main risk factor for RVB is higher hepatic venous pressure gradient (HVPG) [17]. Liu et al. [18] found that the main reason for the development of RVB was the increase in HVPG reaching high figures (≥25 mmHg). The authors of the study noted that neither EVL, nor NSBBs, nor an EVL + NSBBs combination provided reliable prophylaxis of RVB. This is quite understandable due to the following facts. Firstly, EVL has been found to have no effect on the increase in HVPG during CSPH progression [19], and secondly, NSBBs do not reduce HVPG as desired [20]. The in-

Table 2

Comparison of clinical and gender characteristics of EVL + NSBBs and APD patients

Indicator	EVL + NSBBs (n = 150) (%)	APD (n = 27) (%)	Statistical significance
Male gender	85 (56.6%)	15 (55.6%)	$p > 0.05$
Virus-related cirrhosis	72 (48.0%)	13 (48.1%)	$p > 0.05$
Alcohol-related cirrhosis	39 (26.0%)	8 (29.6%)	$p > 0.05$
Other causes of cirrhosis	39 (26.0%)	6 (22.3%)	$p > 0.05$
Esophageal varices, grade 2	40 (26.6%)	7 (25.9%)	$p > 0.05$
Esophageal varices, grade 3	110 (73.4%)	20 (74.1%)	$p > 0.05$
CTP class A	4 (2.7%)	1 (3.7%)	$p > 0.05$
CTP class B	37 (24.7%)	7 (25.9%)	$p > 0.05$
CTP class C	109 (72.6%)	19 (70.4%)	$p > 0.05$

Note: CTP, Child–Turcotte–Pugh; Na, sodium.

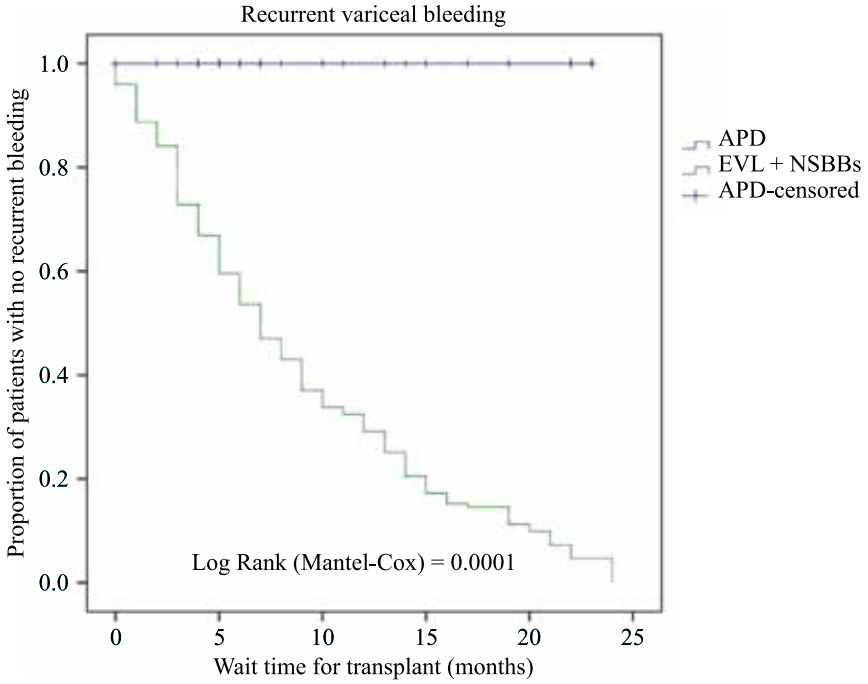

Fig. 1. Proportions of non-RVB patients who underwent APD surgery or received EVL + NSBB therapy (Kaplan–Meier method with Log-Rank test)

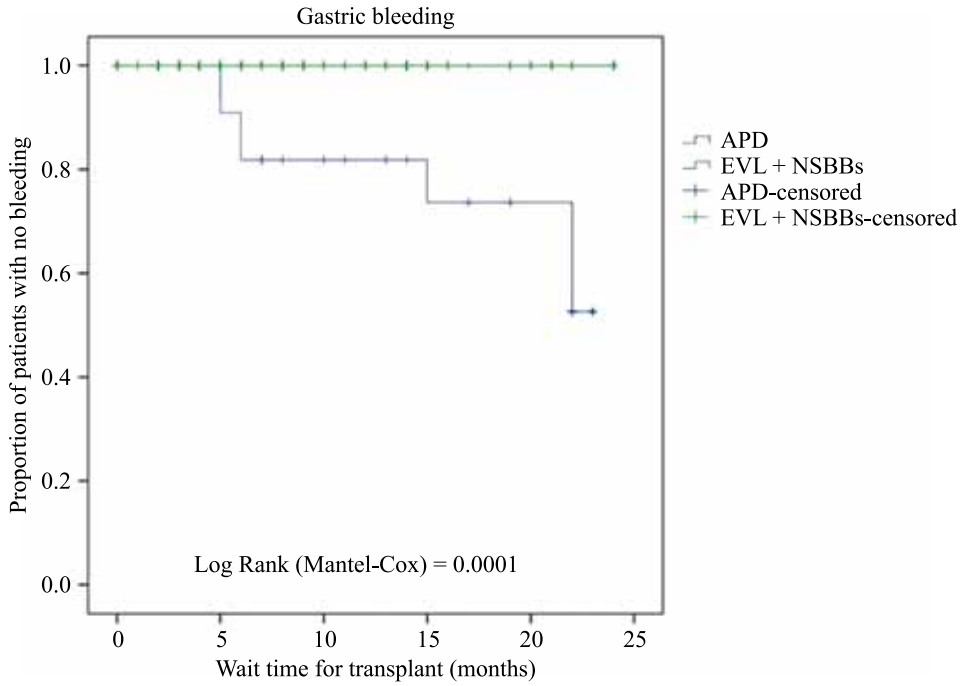

Fig. 2. Proportions of patients with no gastric variceal bleeding who underwent APD surgery or received EVL + NSBB therapy (Kaplan–Meier method with Log-Rank test)

significant level of HVPG reduction with propranolol (10.1–23.2%) and carvedilol (18.6–27.7%) [20] may be due to the lack of response to these drugs in some patients [20, 21].

We believe that the presence of responders and non-responders to NSBBs among patients with CSPH accounts for the reduced effectiveness of secondary prophylaxis of RVB using EVL in combination with beta-blocker administration. Incidence of re-bleeding in non-responders was found to be significantly higher than that in responders of acute hemodynamic response to propranolol use [22].

We discovered that individuals with decompensated cirrhosis who underwent APD surgery did not exhibit RVB during the two-year waiting period for LTx. APD was performed according to the original technique (Russian Federation patent, No 2412657 dated February 27, 2011) [11]. In the past, we have shown that this procedure can effectively prevent rebleeding and result in a three-year absence of recurrent bleeding [23].

However, despite the absence of RVB for 2 years, the present study did reveal the development of recurrent bleeding from gastric varices, which accounted for 48.1% of cases during the specified follow-up period. On the other hand, there was no evidence of gastric variceal hemorrhage associated with the use of EVL plus NSBBs in any case.

The difference in the incidence of gastric variceal bleeding for EVL plus NSBBs and for APD in our opinion is explained by the dynamics of HVPG after these invasive interventions. Abraldes et al. [19] found that EVL does not lead to higher HVPG, while Sinagra et al. [20] found a slight decrease in HVPG after propranolol or carvedilol therapy. Meanwhile, APD operation, disconnecting portocaval connections and reducing blood flow to esophageal varices, does not reduce HVPG and can be complicated by gastric variceal bleeding.

CONCLUSION

APD is an effective method of RVB prophylaxis when alternative treatment, including TIPS implantation or liver transplantation, is not possible.

After performing APD, repeated EGD is necessary for early detection of newly developed varicose veins in the stomach followed by an EVL procedure.

The authors declare no conflict of interest.

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