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MANAGEMENT OF VARICEAL BLEEDING IN THE LIVER TRANSPLANT WAITING LIST

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Objective: to study the outcomes of main surgical methods for stopping and preventing variceal hemorrhage in waitlisted cirrhotic patients. **Material and methods.** In our prospective case-control study, the "case" cohort included 132 patients with cirrhosis complicated by recurrent varicose bleeding, while the "control" group consisted of 92 patients with one episode of bleeding esophageal varices. Treatment included conservative therapy, endoscopic ligation, transjugular intrahepatic portosystemic shunt, and the original azygoportal disconnection technique. **Results.** High MELD scores, severe hepatic encephalopathy, portal vein thrombosis, high degree of varices, and recurrent bleeding significantly affect the mortality of cirrhotic patients. Irrational use of nonselective beta-blocker monotherapy has a negative impact on treatment outcomes. Combined use of drug therapy and surgical methods of stopping and preventing varicose bleeding, reduces the number of relapses, prolongs patients' life to two years or more, which allows to move on to the next stage of cirrhosis treatment – liver transplantation. **Conclusion.** The likelihood of recurrent variceal hemorrhage increases in patients who undergo passive surgical tactics. Azygoportal disconnection should be considered as the operation of choice if the patient has more than one episode of variceal bleeding. Timely and adequate treatment measures, clinical and diagnostic monitoring reduce waitlist mortality.

Keywords: variceal bleeding, liver transplantation, waiting list.

INTRODUCTION

Esophageal varices (EV) are a common clinical manifestation of liver cirrhosis (LC). The incidence of varices in the upper gastrointestinal tract in compensated cirrhosis ranges from 30% to 40%, and in decompensated cirrhosis reaches 60% [1, 2]. In case of variceal rupture, bleeding occurs, the first episode of which is fatal for 20–80% of patients with cirrhosis, and 50–70% of patients have a high risk of recurrence. From the moment of the first episode of variceal bleeding, slightly more than 40% of patients survive for two years [3, 4].

The prognosis of LC depends not only and not so much on age and concomitant disease as by the functional reserve of the liver, the degree and localization of varices, and severity of variceal bleeding [5].

To date, both drugs and various invasive techniques are used to stop bleeding EV and prevent its recurrence [6, 7–9]. However, the ineffectiveness of the former and the lack of radicalism of the others, often forces us to change tactics and resort to open methods of surgical treatment for this category of patients [10, 11]. Shunting, portal blood flow decoupling and resection operations, proposed at different times, improve the quality and prolong the life of patients with cirrhosis to some extent. However, none of these approaches can return portal blood flow to a normal state.

Currently, liver transplantation (LT) remains the only pathogenetically justified method providing long-term positive treatment for LC patients. However, its use is limited by a number of factors, particularly, donor organ shortage [12, 13]. The method often determines the actual waiting time for transplantation, often stretching for several years for 63% of patients [14]. This leads to increased deaths among liver transplant waitlisted patients due to bleeding esophageal varices.

In view of the above, the aim of the study was to study the outcomes of the main surgical methods for stopping and preventing bleeding esophageal varices in patients with liver cirrhosis who are on the waiting list.

MATERIAL AND METHODS

The study was prospective, conducted at Rostov Regional Clinical Hospital, lasting from 2015 to 2020. The data of 224 patients from the LT waitlist, for whom variceal bleeding from the upper gastrointestinal tract became a complication of LC, were analyzed.

Inclusion criteria: esophageal vein dilation (confirmed via imaging); anamnestic evidence of variceal bleeding episodes; evidence of surgical interventions or other actions aimed at stopping or preventing variceal bleeding. There were no specific exclusion criteria. All patients were examined in accordance with the diagnostic protocol for LC patients.

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The study was conducted in two "case-control" groups of patients. The main group "case" included 132 LC patients with recurrent variceal bleeding. The "control" group consisted of 92 patients who had no more than one bleeding EV.

All demographic, clinical and laboratory data for statistical analysis were obtained from a continuously updated electronic database of the Center for Surgery and Donation Coordination of the previously designated institution.

Methods for preventing and stopping bleeding EV included conservative measures, endoscopic variceal ligation, transjugular intrahepatic portosystemic shunt (TIPS) and the original azygoportal disconnection (APD) technique. The essence was resection of the abdominal esophagus and cardiac stomach, followed by formation of esophagogastroanastomosis and creation of anti-reflux cardia [15].

Statistical data analysis was conducted using the IBM SPSS Statistics 23 software. The statistical significance of the differences between compared parameters in normal distribution was assessed by the Student's t-test. In the absence of normal distribution, nonparametric tests were used: Wilcoxon for pairwise comparisons of dependent variables, Mann–Whitney U test, Pearson's chi-square for comparison of independent variables. Differences between compared parameters were considered statistically significant if the error probability was less than 0.05 ($p < 0.05$).

RESULTS

Characteristics of the "case" group

The group of patients with recurrent variceal bleeding consisted of 82 men (62.1%) and 50 women (37.9%). The average age of the patients was within 51 years (49.52 ± 10.92). The waitlist time was 17.14 ± 15.04 months.

Viral hepatitis was the cause of LC in 68 patients (51.5%), alcohol-related liver disease in 31 cases (23.5%), and 17 patients (12.9%) were diagnosed with cryptogenic cirrhosis. Autoimmune diseases and other causes resulted in cirrhosis in 16 patients (12.1%).

During examination, it was established that in 50 patients (37.9%), MELD score did not exceed 20; 64 patients (48.4%) had a MELD score from 20 to 30; in 18 (13.6%) patients, the score exceeded 30 points. In accordance with the Child-Turcotte-Pugh classification for cirrhosis, 126 (95.5%) patients in the group had class C cirrhosis, the rest were class B.

Endoscopic examination of the upper digestive tract showed that 28 patients (21.3%) had esophageal varices grade 1–2, 67 (50.8%) patients had grade 3, while 37 (28.0%) patients had grade 4.

The following were aggravating factors of the underlying disease in patients: overt hepatic encephalopathy – out of 124 (93.9%) patients that had this complication, 57 (43.1%) had grade 3–4; resistant ascites – 57 (43.2%) patients; hepatorenal syndrome – 71 (53.8%) cases; portopulmonary hypertension – 16 (12.1%) patients; thrombosis of the portal vein and its main branches – 27 (20.5%) patients.

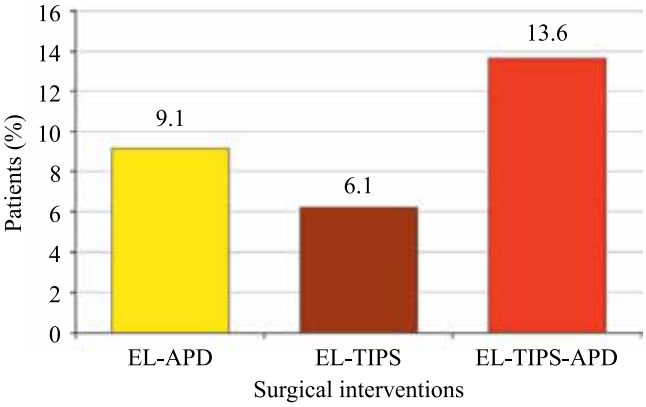

Fig. 1. Distribution of patients by types of surgical interventions: EL – endoscopic ligation; TIPS – transjugular intrahepatic portosystemic shunt; APD – azygoportal dissociation

As noted earlier, all patients in this group were characterized by recurrent bleeding from the esophageal varices. When taking anamnesis, it was found that 101 patients (76.5%) had two to three episodes of bleeding, up to five episodes were recorded in 27 (20.5%) patients, more than five bleeding episodes occurred in 4 (3.1%) patients, with one of them with documented 14 episodes.

With regards to treatment of patients in this group, it should be said that 126 patients (95.5%) received conservative therapy, including non-selective β-blockers. Besides, 77 patients (58.3%) underwent various surgical interventions aimed at stopping bleeding from the EV and preventing its recurrence.

Endoscopic EV ligation was the main type of surgical intervention in 31 patients (23.5%), TIPS in 7 patients (5.3%), 1 patient underwent an original disconnecting surgery. Frequent relapses of bleeding due to failure of endoscopic ligation or portosystemic shunt obstruction made us either resort to the already used techniques repeatedly or perform an open disconnecting surgery (Fig. 1). So, on average, 2.55 ± 1.55 interventions were required per patient in the group.

Despite comprehensive measures taken for the treatment and prevention of variceal bleeding, which were carried out in 76 (57.6%) patients, it still recurred in 38 (28.8%) patients.

Characteristics of the "control" group

Male patients predominated in the control group, as in the main group. There were fewer women – 51 (55.4%) men and 41 (44.6%) women. The average age of the

patients was 53 years (50.48 ± 10.38). Time on the LT waitlist was 15.99 ± 11.87 months.

The main cause of LC in 41 patients (44.6%) in this group was viral hepatitis; LC was a result of alcohol-related liver disease in 20 (21.7%) patients, and in 14 (15.2%) patients, it was autoimmune diseases. Cryptogenic cirrhosis was diagnosed in 14 more patients, congenital and metabolic diseases was the cause of LC in 3 (3.3%) patients.

Laboratory examination established that 49 (53.3%) patients had a MELD score <20; 29 (31.5%) patients had a MELD score within 20 to 30, while 14 (15.2%) patients had a MELD score >30. In accordance with the Child-Turcotte-Pugh LC severity classification, 5 (5.5%) and 87 (94.6%) cases were of classes B and C, respectively.

Endoscopic examination revealed esophageal varices grade 1 and 2 in 55 (59.8%) patients, grade 3 in 31 (33.7%) patients, and grade 4 in 6 (6.5%) patients.

Hepatic encephalopathy with its obvious clinical manifestations was the aggravating factor for 11 (12.0%) patients. Besides, 37 (40.2%) patients had resistant ascites and hepatorenal syndrome, 10 (10.9%) patients had portopulmonary hypertension, 4 (4.3%) cases showed portal vein thrombosis on Doppler ultrasonography.

As noted earlier, patients had one episode of EV bleeding, which characterized the treatment tactics. The main method of treatment was therapy with nonselective β-blockers; 78 (84.8%) patients received the drugs.

Table 1

Main indicators in case and control cohorts (comparative characteristics)

Indicator	Study groups		p
	Case (n = 132)	Control (n = 92)	
Male	82 (62.1%)	51 (55.4%)	0.316
Age (years)	49.52 ± 10.92	50.48 ± 10.38	0.504
MELD score	22.78 ± 6.32	21.41 ± 7.16	0.010
Hepatic encephalopathy (score)	2.47 ± 0.76	2.20 ± 0.75	0.008
Ascites (score)	2.16 ± 0.83	2.12 ± 0.82	0.725
Viral cirrhosis	68 (51.5%)	41 (44.6%)	0.307
Alcoholic cirrhosis	31 (23.5%)	20 (21.7%)	0.760
Child-Pugh class C	126 (95.5%)	87 (94.6%)	0.762
Portal vein thrombosis	27 (20.5%)	4 (4.3%)	0.001
Varicose vein	3.06 ± 0.72	2.40 ± 0.71	<0.001
VB frequency	2.84 ± 1.49	1.00 ± 0.00	<0.001
Waitlist mortality from VB	32 (24.2%)	2 (2.2%)	<0.001
Listing* (months)	17.14 ± 15.04	15.99 ± 11.87	0.524

Note. * length of stay on the liver transplant waiting list. VB – variceal bleeding.

Surgical methods, of which only endoscopic ligation was used, were resorted to in this group only in 6 (6.5%) cases. No other measures aimed at preventing bleeding recurrence or stopping it were taken. This approach resulted in recurrent variceal hemorrhage in 33 (35.9%) patients.

Comparison of indicators in the main and control groups

A comparison of the basic data of patients in both groups showed that a number of indicators had statistically significant differences ($p < 0.05$) (Table 1). This was an evidence of our assumption that patients with recurrent variceal bleeding are in a more severe initial condition. MELD score, severity of hepatic encephalopathy, presence of portal vein thrombosis, degree of EV, and the very fact of variceal bleeding relapse had a significant impact on waitlist mortality rate.

Comparison of the effectiveness of surgical techniques for stopping and preventing variceal bleeding

In the course of the work, we were particularly interested in assessing the effectiveness of each surgical technique used with regard to prevention of recurrent variceal bleeding and reduction of LT waitlist mortality.

Endoscopic EV ligation procedure, which was performed in 75 patients, had a lasting effect in 23 (30.7%) patients only; in 52 patients, varices had to be ligated repeatedly or the surgical tactics had to be changed. So, 6 (8.0%) patients underwent TIPS after several ineffective EV ligation procedures (1.83 ± 0.57) during the first year (6.13 ± 3.26 months); in 7 (9.3%) cases of sequential ligation and TIPS, we eventually had to perform APD, with 2 (2.7%) patients having APD as operation of choice after the second-third bleeding episode.

Of the 33 patients who underwent TIPS, the technique was effective in 28 (84.8%) patients within the first year (6.11 ± 3.08 months). Shunt thrombosis in 5 (15.2%) patients was the reason for a single re-TIPS procedure and one APD operation.

As can be seen, the APD surgery in a series of surgical manipulations performed to stop variceal bleeding becomes the final intervention, giving the patient a chance to avoid recurrent bleeding, stay alive and wait for LT. APD was primarily performed as an independent operation to stop bleeding in only one case, while in 30 (96.8%) cases, it was performed after failures in endoscopic ligation and TIPS.

During the entire follow-up period for patients who underwent APD, which averaged 28 months (0.5–140.8), recurrent variceal bleeding was noted in 3 (9.7%) cases from 0.2 to 63.2 months of follow-up. In spite of another bleeding episode in the life of the patients, they remained

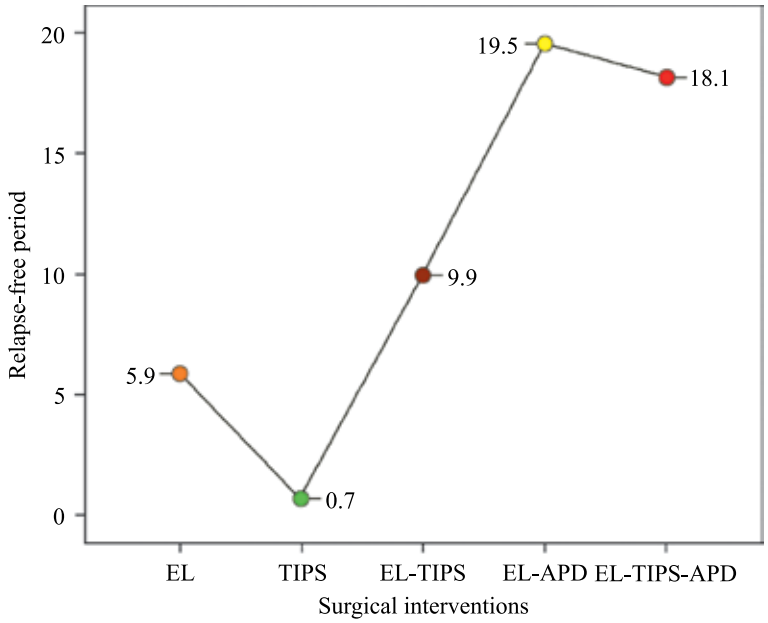

Fig. 2. Average time of variceal bleeding recurrence. One-way analysis of variance. Twenty-four months follow-up. Welch's t-test: value – 8.764; p = 0.001. EL – endoscopic ligation; TIPS – transjugular intrahepatic portosystemic shunt; APD – azygoportal dissociation

alive, including due to liver transplantation performed as soon as possible.

Considering that bleeding from EV can recur, the time of its recurrence with one or another type of surgical intervention was studied (Fig. 2). The analysis showed that the APD surgery allows to postpone the time of recurrence, thereby increasing the patient's time on the LT waiting list.

Analysis of the two-year mortality rate of patients showed that the largest number of patients die when portosystemic shunt is used as a method of stopping and preventing variceal bleeding, while the use of APD, both alone and in combination with other surgical interventions, significantly reduces mortality (Table 2).

The Kaplan–Meier estimator was used to assess patient survival. The two-year LT waitlist survival function in the created model was identified with the development of recurrent variceal bleeding, followed by death (Fig. 3). The significance of the differences between the survival times in the compared groups using different criteria is shown in Table 3.

The average predicted survival time of patients with variceal bleeding when endoscopic ligation and TIPS are used is 15.2 months and 14.3 months, respectively. When endoscopic ligation is used in the first stage of stopping bleeding, followed by TIPS or APD, the average survival time reaches 20.6 months and 20.7 months, respectively. When all the surgical methods we have considered are used, the average survival time will be 19.9 months.

Thus, the use of surgical techniques to arrest and prevent recurrent variceal bleeding certainly increases the patient's LT waitlist survival: 19.9 months with surgical treatment versus 12.9 months without surgery (Log Rank (Mantel-Cox): Chi-square – 9.399; p = 0.002). A significant proportion of patients will not die from bleeding in the next two years, which will give them a chance to move on to the next stage of treatment (liver transplantation) for the underlying disease.

DISCUSSION

The severity of the patient's condition, and, as a consequence, the urgency of a transplant surgery, undoubtedly determines the MELD score. However, in order to

Table 2

2-Year mortality in different methods of surgical treatment of bleeding varicose veins

Surgical intervention	Abs.	%
Endoscopic ligation	8	21.6
TIPS	3	42.9
Azygoportal disconnection	0	0.0
Endoscopic ligation-TIPS	3	37.5
Endoscopic ligation-APD	2	16.7
Endoscopic ligation-TIPS-APD	0	0.0

Table 3

Estimation of survival time differences

Criterion	Chi-square	Degrees of freedom	Significance
Log Rank (Mantel-Cox)	11.270	5	0.046
Breslow (Generalized Wilcoxon)	10.449	5	0.063
Tarone-Ware	11.617	5	0.040

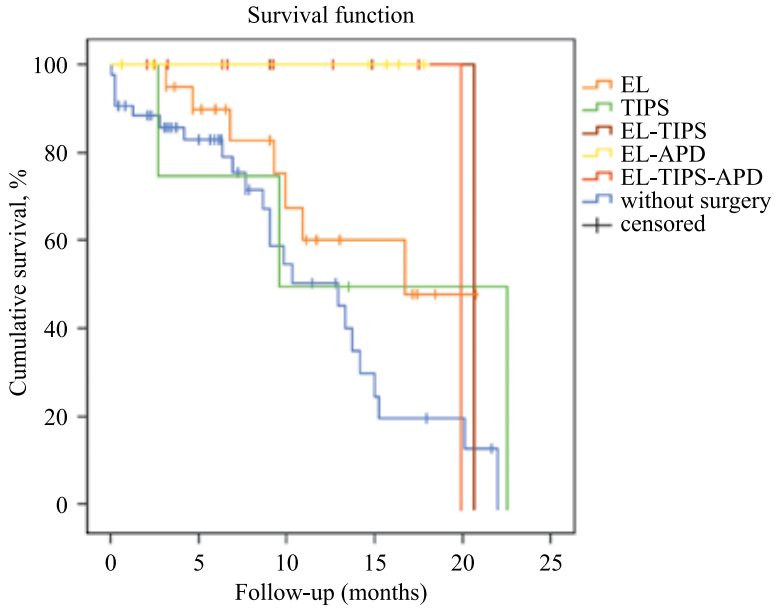

Fig. 3. Survival curves for various surgical methods of stopping and preventing bleeding varicose veins using the log-rank criterion. EL – endoscopic ligation of VRV; TIPS – transjugular portosystemic shunting; APD – azygoportal dissociation

achieve greater patient selection objectivity, especially in the background of recurrent variceal bleeding, each clinical case, in our opinion, should be evaluated separately и.

In addition to MELD, in order to objectively assess the severity of the patient's condition, it is necessary to take into account the degree of EV, number of bleeding episodes, severity of hepatic encephalopathy, and presence of portal vein thrombosis. In turn, the concept of therapeutic prophylaxis requires development of clear criteria for prescribing non-selective β-blockers, since their irrational use can have a negative impact on treatment outcomes in patients.

Syndromic therapy and also timely prevention and treatment of variceal bleeding are the guarantee for long-term management of patients on the liver transplant waitlist. In terms of surgical stopping of variceal bleeding and its prevention, patients with the original APD performed have an advantage. In 12 cases (38.7%), patients achieved stable remission, 7 patients (22.6%) were taken off the waiting list due to positive dynamics in the disease course.

CONCLUSION

Analysis and evaluation of the results of using the main methods for stopping and preventing bleeding from EV in patients with cirrhosis waitlisted for liver transplantation showed that recurrent bleeding occurs primarily in those patients for whom passive surgical tactics are followed. If a patient with EV is on the LT waitlist for a long time and has at least one episode of EV bleeding, APD should be considered as the surgery of choice. A prerequisite for reducing LT waitlist mortality is the timeliness and adequacy of treatment measures and systematic clinical and diagnostic monitoring.

The authors declare no conflict of interest.

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