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The role of variceal bleeding primary prophylaxis in the management of extrahepatic portal vein obstruction in children

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Extrahepatic portal vein obstruction is a major cause of pediatric symptomatic portal hypertension and can lead to profuse variceal hemorrhaging.

Purpose – to evaluate the role of primary prophylaxis of the variceal bleeding in children with extrahepatic portal vein obstruction.

Materials and methods. A one-center prospective cohort clinical study involved 120 patients with extrahepatic portal vein obstruction who underwent primary or secondary variceal bleeding prophylaxis in 2016–2021. The laboratory, ultrasound, and endoscopy data before and after treatment were collected and evaluated.

Results. Variceal bleeding episodes occurred in 5.8% (n=3) of patients who underwent primary prophylaxis and rebleeding occurred in 27.9% (n=19) of those who underwent secondary prophylaxis. Bleeding episodes occurred less frequently in patients from primary prophylaxis group (p=0.013). In patients treated endoscopically (n=53, 44.17%) Variceal bleeding appeared less frequently (n=3, 5.66%) after treatment compared to patients who underwent surgery (n=67 (55.83%), 19 had rebleeding (28.35%)) (p=0.001). In 69.17% patients (n=83) esophageal varices eradication was achieved: in 53.01% (n=44) patients from the primary prophylaxis group and 46.99% (n=39) from the secondary prophylaxis group. Bleeding episodes occurred less frequently after the eradication achievement (p<0.001). The primary prophylaxis led to varices eradication more often than secondary (p=0.003). The varices recurrence episodes rates after the eradication achievement were not different between groups (p=0.51).

Conclusions. Primary prophylaxis can reduce the bleeding risk in extrahepatic portal vein obstruction with high risk of variceal bleeding. The prophylaxis by endoscopic variceal banding is an important bridge in the treatment for pediatric patients with portal hypertension that along with portosystemic shunting could potentially improve prophylactic treatment results.

The Committee on Clinical Investigation of Bogomolets National Medical University approved this study (Protocol No.141, 27.01.2021). All the studies were conducted according to implemented guidelines in consideration of GCP-ICH and Declaration of Helsinki. The written informed consent of all participants' parents/guardians was achieved.

No conflict of interests was declared by the authors.

Keywords: children, portal hypertension, liver, hepatocytes, bleeding, shunt surgery.

Роль первинної профілактики кровотеч у лікуванні допечінкової форми портальної гіпертензії в дітей

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Позапечінкова обструкція ворітної вени є основною причиною симптоматичної портальної гіпертензії та може призводити до профузної варикозної кровотечі.

Мета – оцінити роль первинної профілактики варикозної кровотечі в дітей із допечінковою обструкцією ворітної вени.

Матеріали та методи. В одноцентровому проспективному когортному клінічному дослідженні взяли участь 120 пацієнтів із позапечінковою обструкцією ворітної вени, які пройшли первинну або вторинну профілактику варикозної кровотечі у 2016–2021 рр. Зібрано та оцінено лабораторні, ультразвукові й ендоскопічні дані до та після лікування.

Результати. Варикозна кровотеча виникала в 5,8% (n=3) пацієнтів, які проходили первинну профілактику, а повторна кровотеча – у 27,9% (n=19) пацієнтів, які проходили вторинну профілактику. Кровотечі спостерігалися рідше в пацієнтів групи первинної профілактики (p=0,013). У пацієнтів, які отримували ендоскопічне лігування варикозно розширених вен, рецидив кровотечі виникав рідше (n=3; 5,66%) порівняно з пацієнтами, які перенесли портосистемне шунтування, у 19 (28,35%) випадках яких діагностувалася повторна кровотеча (p=0,001). У 69,17% (n=83) пацієнтів спостерігалася ерадикація варикозу стравоходу: у 53,01% (n=44) пацієнтів групи первинної профілактики та в 46,99% (n=39) пацієнтів групи вторинної профілактики. Епізоди кровотечі виникали рідше після досягнення ерадикації (p<0,001). Первинна профілактика частіше приводила до ліквідації варикозу, ніж вторинна (p=0,003). Частота рецидивів варикозу після досягнення ерадикації не різнилася між групами (p=0,51).

Висновки. Первинна профілактика може знизити ризик кровотечі при обструкції допечінкової ворітної вени з високим ризиком. Профілактика за допомогою ендоскопічного лігування є важливим мостом у лікуванні портальної гіпертензії в дітей, що разом із портосистемним шунтуванням може потенційно поліпшити результати профілактичного лікування.

Дослідження проведено відповідно до впроваджених рекомендацій (Протокол засідання етичної комісії від 27.01.2021 № 141), з урахуванням GCP-ICH і Гельсінської декларації. Отримано письмову інформовану згоду батьків/опікунів усіх учасників дослідження. Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: діти, портальна гіпертензія, печінка, гепатоцити, кровотеча, шунтування.

Introduction

Extrahepatic portal vein obstruction (EHPVO) is a major cause of pediatric symptomatic portal hypertension (PH) in developing countries compared to high-income countries where EHPVO is extremely uncommon [3,18,29]. EHPVO can be idiopathic or secondary to portal vein thrombosis [29]. The etiological factors of portal vein thrombosis are direct injuries to the umbilical vascular system (umbilical vein catheterization, omphalitis, umbilical sepsis), abdominal infection, prothrombotic states, autoimmune systemic disease, vasculitis, or postoperative thrombosis (after liver transplantation or resection) [18]. Variceal bleeding (VB) is a life-threatening complication of PH in children despite the involvement of modern surgical and endoscopic hemostatic techniques [2].

There is no consensus about the necessity of VB primary prophylaxis in children with PH [7], although it is widely used in adults. Primary prophylaxis isn't widely recommended in children nowadays, because the data of beta-blockers usage is limited in pediatric population, the death from the first VB episode aren't frequent and, in addition, in developing countries VB emergency endoscopic or surgical management are mainly available only in tertiary medical centers [19]. However, the VB episode always has severe psychological consequences for both the patient and his parents, especially when hematemesis occurs [6]. According to global guidelines VB secondary prophylaxis should always be performed in children [13]. The meso-Rex surgery is recommended as a main surgical approach to EHPVO but is limited by favorable anatomy presence and surgeon's expertise [7]. Widespread use of surgical treatment methods and long-term study results has led to a better understanding of the causes and consequences of portohepatic circulation in children with PH [15].

Esophagogastroduodenoscopy (EGD) is a standard diagnostic and therapeutic procedure for the detection, treatment, and follow-up of the esophageal and stomach varices [4]. Endoscopic ligation and sclerotherapy can be equally effective methods of a VB prophylaxis.

Therefore, the question of VB prevention timing becomes extremely important.

The purpose of the study – to evaluate the role of primary prophylaxis of the variceal bleeding in children with extrahepatic portal vein obstruction.

Materials and methods of the study

A one-center prospective cohort clinical study involved 120 patients with PH who underwent primary or secondary VB prophylaxis at the Urgent Surgery Department and Endoscopic Department of the National Children's Specialized Hospital «OKHMATDYT» in 2016–2021.

Inclusion criteria were: patient's age 0–18 years, EHPVO, in particular, prehepatic PH, presence of the esophageal varices with high bleeding risk according to the endoscopic data.

Exclusion criteria were: hepatic or posthepatic PH, esophageal varices without bleeding risk, isolated gastric varices, incomplete data, final status unknown.

The EHPVO was confirmed in all patients by ultrasound with a sonographic Doppler study of the portal system. Endoscopic, ultrasound and laboratory data (complete blood count) were collected immediately before starting VB prophylaxis and in the 1, 3, 6, 12 months and then annually after the completion of the treatment.

Table 1

Comparison of the experimental groups' homogeneity according to the primary clinical, laboratory and endoscopic data

Variable	Primary prophylaxis group	Secondary prophylaxis group	P value
Sex (%) Male Female	 33 (63.46%) 19 (36.54%)	 46 (67.65%) 22 (32.35%)	0.777[1]
Age (mean±SD)	6.78±0.63	6.38±0.501	0.611[2]
Platelets count per mm³ (mean±SD)	109±6.86	138.2±11.92	0.043[2]
Leukocytes count per mm³ (median (Q1÷Q3))	4.205 (3.09÷5.01)	3.5 (2.8÷5.50)	0.233[3]
Spleen volume (cm³) (median (Q1÷Q3))	335 (226÷477)	326 (204÷500)	0.763
Esophageal varices grade (%) II III	 38 (73.07%) 14 (26.93%)	 30 (44.12%) 38 (55.88%)	0.003[1]
Gastric varices (%) Yes No	 50 (96.15%) 2 (3.85%)	 64 (94.12%) 4 (5.88%)	0.934[1]
Red wale markings (%) Yes No	 36 (69.23%) 16 (30.77%)	 58 (85.29%) 10 (14.71%)	0.058[1]
PH gastropathy (%) Yes No	 44 (84.61%) 8 (15.39%)	 61 (89.70%) 7 (10.30%)	0.31[1]
Prophylaxis method (%) EVL PSS	 28 (53.84%) 24 (46.16%)	 25 (36.76%) 43 (63.24%)	0.093[1]

Notes: SD – standard deviation; GOV – gastro-oesophageal varices; PH – portal hypertension; EVL – endoscopic variceal band ligation; PSS – portosystemic shunting; 1 – Chi-square test; 2 – Student's T-test; 3 – Wilcoxon W-test.

Depending on the prophylaxis type, patients were divided into two groups. The first group (n=52, 43%) – primary prophylaxis – included patients who underwent endoscopic variceal band ligation (EVL) or different portosystemic shunting (PSS) surgeries in order to prevent VB before the first VB episode occurred. The second group (n=68, 57%) – secondary prophylaxis – included patients who underwent EVL or PSS to prevent recurrence of VB episodes after the initial one had already occurred. All the diagnostic and therapeutic endoscopies were performed by the same endoscopist as well as all the PSS were performed by the same surgeon. Patients underwent endoscopy every 2 month until the eradication was achieved. Next endoscopy repeated after 6, 12 month and then annually.

The median follow-up period for both groups of patients was 22 (Q1÷Q3:9÷33) month, for the primary prophylaxis 24.03±2.148 month, for the secondary prophylaxis 21 (Q1÷Q3:9÷32.5) month.

Studied variables and definitions. High bleeding risk esophageal varices was defined as esophageal varices grade II, according to Japanese Society of Portal Hypertension Second Edition Esophageal Varices Classification [28], combined with gastric varices (GOV) graded GOV1 or GOV2 according to Sarin Classification [27] and/or red wale markings presence [1], or as esophageal varices grade III regardless of gastric varices and/or red wale markings presence. Rebleeding episodes were defined as VB occurrences after secondary prophylaxis realization that demand blood transfusion, Black-More probe placement, urgent endoscopy, or surgery. Varices recurrence is defined as the reappearance of esophageal varices on EGD after successful eradication achievement. Esophageal varices eradication was defined as esophageal varices disappearance or decrease to grade I. Thrombocytopenia was categorized according to platelets reference values as mild (<150000 per mm³), moderate (<100000 per mm³), or severe (<50000 per mm³) [23].

Primary endpoint was the incidence of VB episodes after the primary prophylaxis and rebleeding episodes after the secondary prophylaxis.

Primary outcome was reducing the VB risk by the conducting the primary prophylaxis.

Statistical analysis. The data was analyzed using EZR Statistical Software, v.1.6 (The R Foundation for Statistical Computing). Sample size was detected as 80 patients (40 in each group) with the level of significance (p value) set on 5%, power of the study set on 80% and expected effect size set on 25% according to previous studies [11,24]. Categorical variables were compared using Fisher's exact test. Continuous variables with normal distribution were compared by Student's T-test. Continuous variables with abnormal distribution were compared by Wilcoxon W-test. The level of significance was defined as less than 0.05 ($p \leq 0.05$). A multifactorial analysis utilizing the logistic regression model was performed to determine the factors associated with VB appearance and eradication

achievement. Survival without bleeding episodes was compared between groups by Kaplan–Mayer's analysis.

The Committee on Clinical Investigation of Bogomolets National Medical University approved this study (Protocol No. 141 27.01.2021). All the studies were conducted according to implemented guidelines in consideration of GCP-ICH and Declaration of Helsinki. The written informed consent of all participants' parents/guardians was achieved.

Results of the study

There were 79 (65.83%) males and 41 (34.17%) females among the studied cohort of patients (Table 1). The median age at the time prophylaxis was 6 (Q1÷Q3:3÷9.5) years. The initial manifestations of the PH were VB (n=47, 39.16%), splenomegaly (n=32, 26.67%), abdominal enlargement (n=18, 15%), anemia (n=7, 5.83%), thrombocytopenia (n=5, 4.17%), hepatosplenomegaly (n=5, 4.17%), and abdominal pain (n=5, 4.17%). In one (0.83%) patient portal vein aneurysm was accidentally revealed on the computer tomography of the abdomen.

The main cause of PH and EHPVO was portal vein thrombosis (n=79, 65.83%) due to umbilical vein catheterization during the postnatal period (n=69, 87.34%), omphalitis (n=2, 2.54%), thrombophilia (n=4, 5.06%) and surgical intervention because of hepatoblastoma (n=4, 5.06%), which subsequently caused postoperative portal vein thrombosis. In 41 (34.17%) patients the cause of PH and EHPVO was unknown.

According to the primary clinical, laboratory, and endoscopic data using the chi-square criterion and Student's T-test, homogeneity wasn't detected by the esophageal varices' grade (Chi-square = 8.92, p=0.003) and the platelets count (Student's T-test = 2.07, p=0.043). This difference, although, couldn't bias the study results, because all studied patients had high risk of VB according to endoscopic data and needed the prophylaxis.

Totally, there were 67 PSS performed to our patients with the aim of VB prevention. The PSS type was chosen according to the individual vascular anatomy of the patient. PSS types described in table 2.

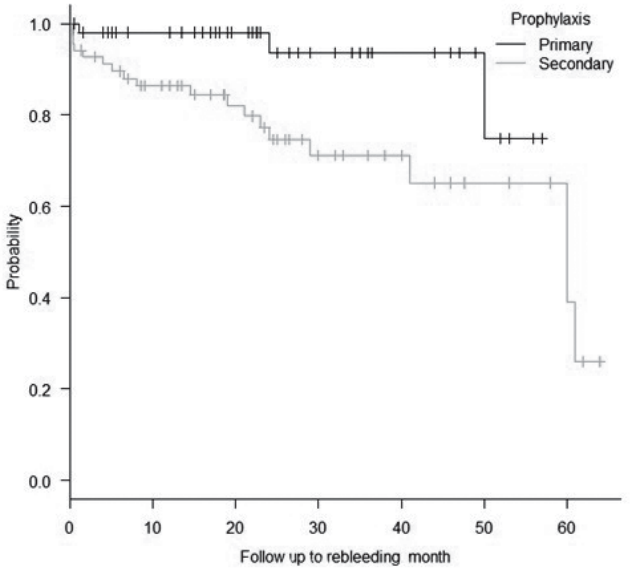

Fig. 1. Probability of VB and rebleeding in primary and secondary prophylaxis

VB episodes occurred in 3 (5.8%) patients from primary prophylaxis group and rebleeding occurred in 19 (27.9%) patients from secondary prophylaxis group after treatment.

Primary prophylaxis was more effective than secondary prophylaxis (Chi-square = 6.1, p=0.013 by the Kaplan–Mayer's method) (Figure 1). The patients in the primary prophylaxis group had a 2-year-survival rate of 93.6±0.05% and a 5-year-survival rate of 74.9±0.17% (median survival was not reached). The patients in the secondary prophylaxis group had a 2-year-survival rate of 74.6±0.06% and a 5-year-survival rate of 39.1±0.15% (median survival was 60 months 95% CI 41 months – ∞).

In patients of both groups treated endoscopically (n=53, 44.17%) VB episodes and rebleeding appeared less frequently (n=3, 5.66%) compared to those ones, who underwent surgical treatment (n=67 (55.83%), 19 (28.35%) had VB (p=0.001 by the Fisher's exact test). In the first group VB occurred in 0 patients treated by EVL (total number = 28) and in 3 (12.5%) patients treated by PSS (total number = 24). In the second group rebleeding oc-

Table 2
Types of portosystemic shunts which were performed in patients

PSS type	Primary prophylaxis (n=28)	Secondary prophylaxis (n=43)	Total (n=67)
Rex-shunt	3	9	12
Spleno-renal shunt	11	14	25
Proximal spleno-renal shunt	1	0	1
Distal spleno-renal shunt	1	10	11
Spleno-suprarenal shunt	5	4	9
Meso-caval shunt	3	5	8
Meso-renal shunt	0	1	1

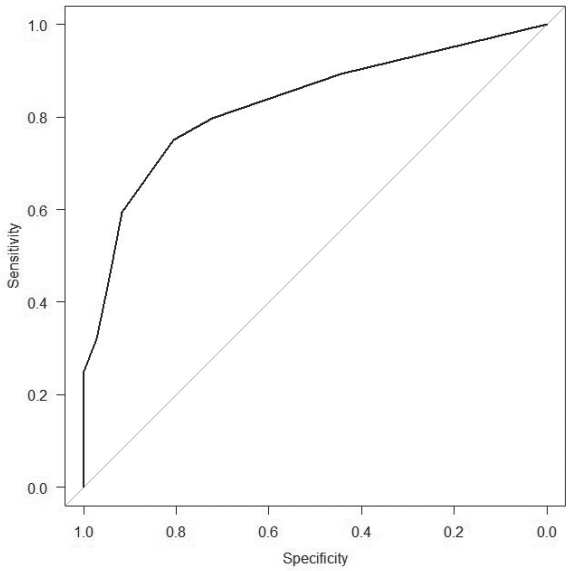

Fig. 2. ROC-curve of the model parameters. Area under curve 0.814 (95% CI 0.74-0.889)

curred in 3 (12%) patients treated by 3 (Q1:Q3:1÷3) EVL sessions (total number of patients treated by EVL = 25) within 11±5.132 month after treatment, and in 16 (37.21%) patients treated by PSS (total number = 43).

There wasn't found any difference in VB episodes and rebleeding rates between Rex-shunt and other PSS types for primary prophylaxis group (Chi-square=0,00, p=0,974) as well as for secondary prophylaxis group (Chi-square=0,13, p=0,717).

Varices eradication was achieved in 83 (69.17%) patients: 44 (53.01%) patients from the primary prophylaxis group and 39 (46.99%) patients from the second group. The primary prophylaxis led to varices eradication more often than secondary (Chi-square=9.03, p=0.003).

Among those patients, who achieved the eradication (n=83, 69.17%), bleeding episodes occurred in 4 (3.33%) individuals: 1 due to portal hypertensive gastropathy, 1 due to gastric varices, and 2 due to recurrent esophageal varices. Among those patients who had not achieved the eradication (n=37, 32.83%), bleeding episodes occurred in 18 individuals. It was found that VB occurred less frequently after the eradication achievement (p<0.001 by the Fisher's exact test).

In patients of both groups who were treated endoscopically (n=53, 44.17%) eradication was achieved more frequently (n=50, 94.33%) compared to those who were treated surgically (total number = 67 (55.83%), number of eradication achievements = 33 (49.25%)) (p<0.001 by the Fisher's exact test). In particular, the first group eradication was not achieved in 1 (3.57%) patient treated by EVL (total number = 28) and in 7 (29.17%) patients treated by PSS (total number = 24). In the second group eradication wasn't achieved in 2 (8%) patients treated by EVL (total number = 25) and in 27 (62.79%) patients treated by PSS (total number = 43). A statistically significant difference between EVL and PSS methods of eradication was found for primary (Chi-square=4.69, p=0.03) and secondary (Chi-square=15.86, p<0.001) prophylaxis groups.

In patient treated by EVL, the eradication was achieved by 3 (Q1:Q3:2÷3) banding sessions in primary prophylaxis group and by 3 (Q1:Q3:2÷4) banding sessions in secondary prophylaxis group.

There wasn't found any difference in esophageal varices eradication achievement between Rex-shunt and other PSS types for primary prophylaxis group (Chi-square=0.17, p=0.68) as well as for secondary prophylaxis group (Chi-square=0.00, p=0.948).

The logistic regression model analysis was done and ROC-curve was built to detect factors associated with the eradication achievement (Table 3 and Figure 2). Results revealed that VB presence in anamnesis (OR=0.28 (95% CI 0.11–0.77), p<0.001) and the prophylaxis method (PSS) (OR 0.33 (95% CI 0.12–0.93), p=0.036) decreased the eradication achievement odds.

After the eradication achievement the varices recurrence occurred in 10 (12.05%) patients: 4 (40%) from the primary prophylaxis group and 6 (60%) from the secondary. The varices recurrence episodes were not statistically different between groups (p=0.51). Among patients from the first group the varices recurrence episodes appeared in 3 (11.11%) patients treated by EVL (total number = 27), and in 1 (5.88%) treated by PSS (total number = 17). Among patients from the second group the varices recurrence episodes appeared in 3 (13.04%) patients treated by EVL (total number = 23) and in 3 (17.65%) treated by PSS (total number = 17). The statistically significant difference was not found by Chi-square test in both groups in regard

Table 3
Coefficients of the three-factors eradication achievement prognostic model in studied patients

Factor	OR	Lower 95% CI	Upper 95% CI	P-value
VB presence in anamnesis	0.288	0.107	0.774	<0.001
Esophageal varices' degree	0.548	0.212	1.420	0.215
Prophylaxis method (PSS)	0.336	0.121	0.931	0.036

Notes: OR – odds ratio; CI – confidence interval; VB – variceal bleeding.

to varices recurrence (for first group Chi-square=0.00, p=0.962, for second group Chi-square=0.00, p=0.965).

Discussion

Despite, the VB primary prophylaxis is widely conducted in adult population with PH, there is no consensus about it in pediatric population [6]. Esophageal varices are present in 90–95% of patients with EHPVO [14]. M. Duche et al. reported that 96% of children with PH and spontaneous VB episodes had esophageal varices grade III, or esophageal varices grade II with red wale markings and/or gastric varices extending to the cardia on EGD [11]. Oliveira et al. reported that the medium and large caliber of esophageal varices increased the VB risk in children with EHPVO [21]. In our study all of our patients had the varices with high risk of variceal bleeding according to the endoscopic data.

R. Khanna et al. claimed that EHPVO is responsible for up to 80% of the pediatric upper gastrointestinal bleeding episodes due to the rupture of esophageal and gastric varices [2,18]. Morbidity and mortality, as a result of VB, remain high. Eroglu et al. reported about 19% mortality during the first 35 days after VB appearance in children with chronic liver diseases [12]. Therefore, the importance of VB prevention in children with PH should not be underestimated.

Despite the absence of the consensus according to VB primary prophylaxis in children with EHPVO, different studies showed that treatment of high bleeding risk varices can potentially improve the outcomes and life quality in patients with different etiology PH [9–11,22,26,30]. J.R. Pimenta et al. said that primary prophylaxis should be conducted in the setting of endoscopic sings of the high VB risk [24]. M. Duche et al. reported that chances of a 10-year-survival after successful primary prophylaxis was established at the level of 96% for non-cirrhotic PH patients and 72% for cirrhotic PH [11]. Our study showed that primary prophylaxis can reduce the chances of VB in patients with EHPVO. VB episodes occurred in 5.8% of patients who underwent primary prophylaxis and rebleeding occurred in 27.9% of those who underwent secondary prophylaxis.

Rebleeding rates according to literature data ranges between 24% and 42% were discovered in patients treated with PSS [16,20]. At the same time, patients who were treated with EVL showed lower rebleeding rates and higher eradication rates [5,17,25,30]. Our data analysis revealed that the primary prophylaxis using EVL increased the rate of eradication achievement, which could be explained by EVL direct effect on the varices. EVL does not affect the pressure in the portal system, thus it cannot become a definitive treatment of EHPVO. In case of splenomegaly, sooner or later the question of PSS, in particular meso-Rex bypass, will arise. When meso-Rex shunt performing is not possible, EVL could be an effective and available primary or secondary VB prophylaxis option. Although EVL couldn't become an alternative for PSS, it could become a reliable supplementation for PSS, what could potentially provide lower rebleeding rates and improve prophylactic treatment results and quality of patient life.

Similarly to other cohort studies, this study has a few limitations. One of the limitations of our study is absence of homogeneity in the esophageal varices degree in the studied groups. Although all our patients had a signs of high bleeding risk [11,24] and had to undergo VB prevention treatment [8]. Another limitation is a comparison endoscopic variceal banding with PSS surgery. It is well known fact that endoscopic methods have a direct influence on the varices, but with a temporary effect due to disability of portal pressure reducing. However, it is important to use endoscopy in case of acute variceal bleeding as well as when PSS, in particular Rex-shunt, isn't available or effective. We offer this comparison in order to investigate the efficacy of EVL and possibility to use it along with PSS in treatment of EHPVO in children. Different types of PSS performed to our patients because of their vascular anatomy features also can limit our results. Subsequently, further randomized control studies are needed in order to minimize all potential biases and make a consensus in VB primary prophylaxis usage in pediatric population with PH.

Conclusions

Primary prophylaxis should be performed in EHPVO patients with high risk of VB because it can reduce the bleeding odds. According to Kaplan-Mayer's method, primary prophylaxis is more effective than secondary (median survival for the primary prophylaxis was not reached during observation period). The question of using endoscopic treatment remains debatable because this method is temporary, does not affect the pathophysiological branches, and does not eliminate a possible VB cause. Concurrently, the endoscopic prophylaxis is an important bridge in the treatment for pediatric patients with PH, that along with PSS could potentially provide frequent eradication achievement, lower rebleeding rates and improve prophylactic treatment results.

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No conflict of interests was declared by the authors.

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