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Endoscopic variceal bleeding prophylaxis in children with cirrhotic portal hypertension

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Cirrhotic portal hypertension (CPH) is an increase in intravascular pressure in the portal vein due to increased resistance of the liver parenchyma in so-called «cirrhotic liver diseases». In the context of the pretransplantation period, endoscopy is focused on the prevention or management of bleeding from esophageal varices, which are present in 40–60% of patients with CPH.

Aim – to analyze our experience of bleeding control by means of endoscopic options in children with CPH, optimizing the timing for procedures and ways to reduce the recurrent bleeding in the course of pretransplant management.

Materials and methods. A total of 303 case histories were analyzed retrospectively in the period from January 2011 to December 2023; 63 (22.4%) patients with CPH were identified. Patients were divided into 2 groups: a prospective study (n=43; 68.2%) and a control group (n=20; 31.8%).

Results. The most common causes of CPH were: idiopathic fibrosis (n=17; 26.9%), and biliary atresia (n=12; 19.1%). High-grade esophageal varices were revealed in 46 (73.1%) children, and 19 (30.1%) children had bleeding episodes. 20 patients underwent endoscopic band ligation. The endoscopic band ligation allowed for the reduction of the varices to grade I in 5 (25.0%) patients, while no significant influence on patients with high-grade varices number was achieved. Endoscopic sclerotherapy was performed in 6 (13.9%) children without a significant effect on the varices grade.

Conclusion. Endoscopic band ligation allowed for the reduction of the varices grade in a small number of patients in the prospective study group. Endoscopic sclerotherapy is useful where a ligation device cannot be transferred through the esophagus, though it did not significantly affect the number of patients with high-grade esophageal varices. In children with CPH screening endoscopy is mandatory, especially for those who are listed for liver transplantation.

The study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee of the institution mentioned in the paper. The informed consent of parents (or their guardians) and children was obtained for the study.

The author declares no conflict of interest.

Keywords: cirrhotic portal hypertension, bleeding, endoscopic band-ligation, endoscopic sclerotherapy, liver transplantation, children

Ендоскопічна профілактика кровотечі з варикозно-розширеніх вен стравоходу в дітей із печінковою формою порталної гіпертензії

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Печінкова форма порталної гіпертензії (ППГ) – це збільшення внутрішньосудинного тиску у ворітній вені через підвищений опір паренхіми печінки при так званих «циротичних захворюваннях печінки». У контексті передтрансплантаційного періоду ендоскопія

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є корисною для обстеження пацієнтів та спрямована на профілактику або лікування кровотечі з варикозних вен, які присутні у 40–60% пацієнтів із ППГ.

Мета – проаналізувати власний досвід контролю кровотечі за допомогою ендоскопічних методів у дітей із ППГ, знайти оптимальний час для процедур та способи досягнення відсутності рецидивних кровотеч під час передтрансплантаційного ведення.

Матеріали та методи. Ретроспективно проаналізовано 303 історії хвороби в період із січня 2011 року по грудень 2023 року, виявлено 63 (22,4%) пацієнти з ППГ. Пацієнтів було розподілено на 2 групи: проспективного дослідження (n=43; 68,2%) та групу контролю (n=20; 31,8%).

Результати. Серед найпоширеніших причин, що привели до розвитку ППГ, були: ідіопатичний фіброз (n=17; 26,9%) та атрезія жовчних шляхів (n=12; 19,1%). Ендоскопічно варикозні вени стравоходу високого ступеня виявлено в 46 (73,1%) дітей, у 19 (30,1%) спостерігалися епізоди кровотеч. 20 пацієнтам було проведено ендоскопічне лігування. Процедура ендоскопічного лігування дала змогу зменшити ступінь варикозного розширення вен до I ступеня у 5 (25,0%) пацієнтів, тоді як значущого зменшення кількості пацієнтів із варикозним розширенням вен високого ступеня досягнуто не було. Ендоскопічну склеротерапію було проведено у 6 (13,9%) дітей без суттєвого впливу на ступінь варикозно розширеніх вен.

Висновок. Ендоскопічне лігування дало змогу знизити ступінь варикозно розширеніх вен у невеликої кількості пацієнтів проспективної групи дослідження. Ендоскопічна склеротерапія у маленьких пацієнтів із ППГ є корисною, коли лігуючий пристрій не може бути проведений через стравохід, але вона суттєво не вплинула на кількість пацієнтів із варикозом високого ступеня. У дітей із ППГ скринінгова ендоскопія є обов'язковою, особливо для тих, хто перебуває в листі очікування трансплантації печінки.

Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено Локальним етичним комітетом зазначененої в роботі установи. На проведення досліджень отримано інформовану згоду батьків (або їхніх опікунів), дітей. Автор заявляє про відсутність конфлікту інтересів.

Ключові слова: печінкова форма порталної гіпертензії, кровотеча, ендоскопічне банд-лігування, ендоскопічне склерозування, трансплантація печінки, діти.

Introduction

Cirrhotic portal hypertension (CPH) is an increase in intravascular pressure in the portal vein due to increased resistance of the liver parenchyma in the so-called «cirrhotic liver diseases», among which biliary atresia [21], idiopathic fibrosis [11], autoimmune hepatitis, and cystic fibrosis [2] can be mentioned. Esophageal varices are present in 40–60% of patients with CPH [3]. The most threatening complication of esophageal varices is their rupture with bleeding [7,16]. Mortality from bleeding associated with rupture of esophageal and gastric varices in children remains high, estimated at 5–19%, despite the use of modern methods of surgical and endoscopic hemostasis [15]. In the context of pretransplantation and posttransplantation periods, endoscopy is useful for the evaluation of patients, focused on the prevention or management of gastrointestinal bleeding [4]. At the same time, the question of the feasibility of screening endoscopy in children to detect varices remains open [22], and there is no single view on the effectiveness of primary endoscopic prophylaxis of esophageal variceal bleeding [6], while other authors state that bleeding preventive therapy in the patients with high-risk varices can significantly improve the quality of management and life in children with portal hypertension of any etiology [8].

Aim: to analyze our own experience of bleeding control by means of endoscopic options in children with CPH, finding the optimal timing for procedures and ways to achieve the absence of recurrent bleeding in the course of pretransplant management.

Materials and methods of the study

Patients' data were collected from case records retrospectively. 303 case histories were analyzed in the period from January 2011 to December 2023, and 63 (22.4%) patients with CPH were identified.

The patients were divided into two groups: the prospective study group included 43 (68.2%) children with CPH who underwent diagnostic and surgical procedures and follow-up between 2019 and 2023. The control group consisted of 20 (31.8%) children treated between 2011 and 2018. The time frame chosen for the distribution of patients into groups is due to the appearance of the entire spectrum of endoscopic procedures in the clinic in 2018, while before this year, endoscopy served mainly as a diagnostic examination.

For all patients, the following criteria were analyzed: underlying pathology, age of onset, gender, variceal bleeding episodes, endoscopic examinations and procedures (initial and following varices grade, variceal band ligation procedures, and endoscopic sclerotherapy), the result of endoscopic prophylaxis.

The examination data used for analysis was as follows: endoscopy was performed in all patients (n=63) to assess the grade of esophageal varices, gastric varices and gastric mucosa, and to perform variceal band ligation, if necessary, using endoscopes GIF-H185, GIF-Q150, GIF-XQ260, Olympus LTD, Japan, and ligation devices Boston Scientific, Cook Medical Incorporated, Mar Flow, Micro-Tech with capacity of 6–7 ligature rings per cassette. In sclerotherapy, the sclerosant is injected directly into the varicose vein (intravasally) using an endoscopic

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Table 1

Initial demographic and clinical characteristics of studied patients of both groups

Characteristic	Prospective study group (n=43)		Control group (n=20)		p
	N	%	N	%	
Gender (male/female)	23 / 20	53.4/46.6	12 / 8	60/40	0.833 ¹
Median age, years (95% CI)	11 (7–12)	-	8 (6–10)	-	0.211 ²
Bleeding episode as initial CPH sign (yes/no)	13 / 30	30.2/69.8	6 / 14	30/70	0.783 ¹
Other bleeding episodes (yes/no)	8 / 35	18.6/81.4	5 / 15	25/75	0.804 ¹
Esophageal varices grade II	19 / 24	44.2/55.8	6 / 14	30/70	0.005 ¹
Esophageal varices grade III	14 / 29	32.5/67.5	11 / 9	55/45	0.156 ¹
Gastric varices (yes/no)	24 / 19	55.8/44.2	17 / 3	85/15	0.048 ¹

Notes: 1 – Chi-square test; 2 – W-Wilcoxon test.

needle that is passed through the working channel of the endoscope [11]. In children, 23–25 G needles are used. For the treatment of variceal bleeding, N-butyl-2-cyanoacrylate (Histoacryl glue) was used. It polymerizes into a solid mass upon contact with ionic materials, including blood. A therapeutic endoscope with a 3.7 mm working channel was used to inject the glue to ensure accurate positioning of the injection catheter and a 23G endoscopic needle. The esophageal varices grade was assessed according to the Japanese Research Society for Portal Hypertension [19], and gastric varices were graded according to the Sarin classification [18].

Statistical analysis was performed using EZR (R-statistics). A P-value <0.05 was considered statistically significant. Data distribution was compared using the Chi-square test or the Wilcoxon criteria. The McNamara test with Yates Correction was used to compare the follow-up results of endoscopic treatment. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to quantify the strength of associations.

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

Results of the study

Patients who manifested CPH as a part of the natural course of the end-stage liver diseases (ESLD) had their primary diagnosis established in the centers of hepatology, orphan disease, pediatrics, or nephrology, and were referred to the surgical clinic upon the appearance of splenomegaly, hypersplenism, primary diagnostic endoscopy that revealed esophageal varices, or after an initial bleeding episode in 35 (55.6%) cases. In the remaining 28 (44.4%) cases, patients were initially admitted to the

surgical clinic. The follow-up period of the studied patients was 6–128 months, median 39.5 (95% CI: 34–49).

Among the most common causes leading to the development of CPH were: idiopathic fibrosis (n=17; 26.9%), biliary atresia (n=12; 19.1%), hepatic fibrosis combined with polycystic kidney disease (n=11; 17.4%), autoimmune hepatitis (n=10, 15.9%), cystic fibrosis (n=5; 7.9%), hepatitis B (n=2; 3.4%), and with micronodular cirrhosis, multiple arteriovenous malformations of the liver, Niemann–Pick disease, Wilson disease, Caroli disease, primary sclerosing cholangitis – (n=1; 1.7%) each.

Among the primary clinical manifestations of CPH were bleeding episodes (n=19; 30.1%), high-grade esophageal varices (n=46; 73.1%), hypersplenism (n=58; 92.1%), and splenomegaly occurred in all patients (n=63; 100%). In (n=43; 21.6%) children, gastric varices were detected initially, without bleeding episodes in the anamnesis. Among the manifestations of the ESLD in patients of the CPH group, encephalopathy (n=30; 47.6%), ascites (n=26; 41.2%), jaundice (n=17; 26.9%) were generally observed. Detailed characteristics (before treatment) and clinical data of the studied patients of both groups are given in Table 1.

In the studied CPH patients of the prospective and the control groups, no difference in the gender proportion of the groups (p=0.573), and no significant difference in the median age at the time of CPH diagnosis (p=0.211) were found, therefore the groups were considered as uniform and available for comparison.

When comparing clinical presentation, no significant difference was detected in the proportion of patients with bleeding episode as the first sign of CPH (p=0.783), as well as in the proportion of patients with endoscopically detected high-grade III varices (p=0.156).

In the CPH patients of control group, endoscopy was used for a screening examination only in 16 (80.0%) patients (Figure A), while 4 (20.0%) children underwent endoscopic band ligation. In the 43 (68.2%) children of

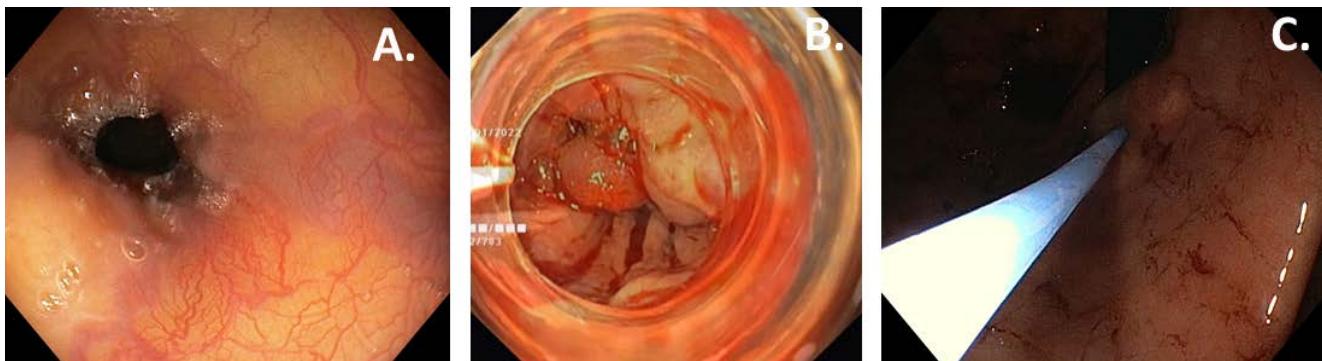


Fig. Endoscopic presentation of studied patients: A – *Patient D*, 2 y.o., biliary atresia, esophageal varices grade I. Icteric mucosa; B – *Patient T*, 15 y.o. Primary sclerosing cholangitis. Acute bleeding management by means of band ligation; C – *Patient P*, 5 m.o., biliary atresia. Acute bleeding management by means of Histoacryl injection into the gastric varix

the prospective study group, the following endoscopic methods of bleeding prevention were used: endoscopic band ligation in 20 (46.5%) patients (Figure B), endoscopic sclerotherapy in 6 (13.9%) patients (Figure C), and endoscopic prophylaxis was not performed in 17 (39.5%) patients.

Of the 20 (46.5%) patients who underwent endoscopic band ligation from 1 to 6 procedures were performed, with a median of 2 (95% CI: 1–3) sessions. In 7 (35.0%) patients, recurrences of bleeding after the primary endoscopic band ligation procedure occurred, and in 2 (28.5%) children, there were repeated recurrent bleeding episodes. The results of endoscopic band ligation of esophageal varices in patients with CPH in patients of the prospective group are presented in Table 2.

The endoscopic band ligation procedure allowed to reduce the degree of varicose veins, reducing it to grade I in 5 (25.0%) patients ($p<0.001$), while no significant indicators were achieved for reducing the number of pa-

tients with high-grade varicose veins ($p=0.815$ and $p=0.701$). Complete eradication was not achieved in any of the patients.

Endoscopic sclerotherapy was performed in 6 (13.9%) children as part of pretransplantation management. The choice of the method in patients with biliary resulted from the patients' age and weight parameters, and the diameter of the esophagus, did not allow the cap of the ligation device to be inserted into the esophagus in (n=5) cases, and as additional therapy in combination with endoscopic band ligation in (n=1) patient with a vascular tumor of the liver due to persistent high-grade varices and repeated bleeding from them. Repeated procedures in 3 (50%) patients were performed at the height of bleeding in order to stop it.

The results of endoscopic sclerotherapy in patients with CPH are presented in Table 3.

The small number of patients does not allow for obtaining the statistically significant results. A decrease in

Table 2

Comparison of primary and final endoscopic data of patients with CPH (n=20) of prospective group, who underwent endoscopic band ligation, number of patients (%)

Characteristics	Initial results	Final results	p
Grade of esophageal varices:			
0	0 (0%)	0 (%)	–
I	0 (0%)	5 (25.0%)	<0.001 ¹
II	8 (40.0%)	10 (50.0%)	0.815 ¹
III	12 (60.0%)	5 (25.0%)	0.701 ¹

Note: 1 – McNamara test with Yates Correction

Table 3

Comparison of initial and final endoscopic data in patients with CPH (n=6) of prospective group, who underwent endoscopic sclerotherapy, number of patients (%)

Characteristics	Initial results	Final results	p
Grade of esophageal varices:			
0	0 (0%)	0 (0%)	–
I	0 (0%)	0 (0%)	–
II	4 (40.0%)	3 (50.0%)	1.0
III	2 (60.0%)	3 (25.0%)	1.0

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Comparison of primary and final endoscopic data of patients with CPH (n=4) of control group, who underwent endoscopic band ligation, number of patients (%)

Characteristics	Initial results	Final results	p
Grade of esophageal varices:			
0	0 (0%)	0 (%)	1
I	0 (0%)	3 (75.0%)	1
II	2 (50.0%)	1 (25.0%)	1
III	2 (50.0%)	0 (0%)	1

the varices grade was not observed. The endoscopic sclerotherapy procedure did not have a significant effect on the varices grade in the studied patients; in 3 (50%) patients who underwent sclerotherapy, recurrent bleeding was observed, which was associated with a rapid irreversible deterioration of the liver parenchyma due to the course of the underlying ESLD, biliary atresia in most presented cases, which maintained the high intrahepatic parenchymal resistance and, accordingly, increased the pressure in the portal system. No complications of endoscopic sclerotherapy were observed in the studied group of patients.

12 (27.9%) patients from the prospective study group, to 8 (75.0%) patients of which endoscopic methods were applied, were subsequently successfully transplanted. 8 (18.6%) patients of prospective group patients were included in the liver transplantation waiting list at the time of study completion.

In the control group of patients with PPG, endoscopic band ligation was used in 4 (20.0%) patients, and endoscopic prophylaxis was not performed (n=16; 80.0%). Of the 4 (20%) patients who underwent endoscopic ligation as a method of primary prevention of bleeding from esophageal varices in the preoperative period, ligation procedures were performed from 1 to 4, median 2 (95% CI: 1–3) sessions. All patients had undergone previously a surgery (Kasai procedure n=1, splenectomy n=1, distal splenorenal shunt n=1, splenorenal shunt n=1), and received endoscopic band ligation to achieve control over residual esophageal varices.

The results of endoscopic esophageal varices band ligation of CPH patients in the control group are presented in Table 4.

The small number of patients does not allow for obtaining the statistically significant results. Nevertheless, endoscopic band ligation in previously operated patients allowed to reduce the degree of varicose veins to grade I in 3 (75.0%) patients, and to reduce the number of patients with high-grade varices. No variceal bleeding recurrence was observed in CPH patients of the control group. 3 (75%) of these patients were included in the liver transplantation waiting list at the time of study completion.

Discussion

CPH in the pediatric population can result from numerous liver diseases, and when reaching the end stage, it brings additional life-threatening complications, such as variceal bleeding [3,4,19]. In the course of the pre-transplant period, variceal bleeding is most feared, as when it takes place, it deteriorates the patients' condition and influences the outcome of the transplant procedure [2,9,22]. In recent years, many publications have been devoted to endoscopic prophylaxis methods and their undoubtedly success in improving the quality of life, including patients with CPH [6,7,16]. On the one hand, endoscopic prophylaxis methods in the treatment of portal hypertension allow to achieve control over bleeding without affecting the portal perfusion of the liver, unlike surgical shunting procedures. On the other hand, they are not radical and long-term, which is especially true for patients with CPH.

By most authors, it is stated that the most common causes of cirrhosis in the first years of life are biliary atresia and genetic-metabolic diseases, whereas in older children, cirrhosis is usually caused by chronic viral hepatitis and autoimmune diseases [13,21]. In the studied group, CPH was also the result of many different etiological factors, but idiopathic liver fibrosis took the first place (n = 17; 26.9%), and biliary atresia was only the second (n = 12; 19.1%). This can be explained by the fact that the number of patients with biliary atresia who were treated at the study center was actually larger, but those patients did not meet the inclusion criteria for the minimum allowable observation period due to, in most cases, critical deterioration of the condition and the absence of a transplant program in the early stages.

Undoubtedly, patients with terminal liver diseases are primarily considered as potential candidates for transplantation, or in light of the treatment of their underlying diseases [1]. The problem of portal hypertension and its most threatening manifestation, variceal bleeding, is most often highlighted by authors of publications devoted to children with biliary atresia [5,19], and the risk of mortality from such bleeding in this population of children [5,6,22].

The overall incidence of variceal bleeding in children is not well presented in the current scientific literature.

Variceal bleeding in children with biliary atresia occurred in approximately 20% of those who did not require liver transplantation in a retrospective cohort study spanning 20 years [17]. More recent results are reflected in a cohort retrospective study arranged by the Biliary Atresia Consortium, which reported three episodes of variceal bleeding during the first 2 years of life in 104 children with biliary atresia, 50% of whom required transplantation during this period, i.e., were in the decompensated stage of the disease [20].

The observations based on our study are interesting: children with biliary atresia did not become the dominant group by etiological factor; moreover, in the group as a whole, unlike patients with the prehepatic form of portal hypertension, the initial manifestation of CPH in the form of bleeding was observed only in the 25.9% of children in the group. Patients with biliary atresia had recurrent episodes of variceal bleeding before surgical treatment.

The study of M. Duche et al. [6] showed that spontaneous bleeding is accompanied by complications that threaten the patient's life in approximately 20% of cases, and the risk of death from the first bleeding is significant in children with liver cirrhosis. The same investigator reported in a cohort of over 1,300 patients that the 10-year bleeding-free rate after primary prophylaxis for high-risk portal hypertension was 96% in noncirrhotic portal hypertension and 72% in CPH. The 10-year overall survival rates were 100% and 93%, respectively. In children with cirrhosis who do not require liver transplantation in the near future, primary prophylaxis of bleeding with endoscopic methods is the most appropriate choice when high-risk portal hypertension is present [4,6,16].

A large retrospective study of data from a single pediatric surgical center with transplantation capabilities, which included patients treated for 20 years [10], was conducted to determine the feasibility of screening endoscopy in patients with CPH awaiting transplantation. The authors demonstrated that the presence of varices does not significantly affect the timing of transplantation. However, 30% of patients with ESLD require one or more endoscopies before transplantation in order to perform endoscopic prophylaxis of variceal bleeding. The results show that the frequency of endoscopic intervention, the frequency of rebleeding in the interval between the initial endoscopy and possible liver transplantation, as well as the need for repeated examinations and procedures, were significantly higher in the group of children in whom the first endoscopy was performed for urgent indications, and not as a planned screening.

Similar results are demonstrated by our study: during the waiting period for transplantation, patients in the

prospective group encountered repeated episodes of variceal bleeding, which, in turn, required repeated endoscopic interventions.

There are studies underway to find some indirect ways to predict the presence of high-grade esophageal varices in patients with CPH. For example, splenomegaly and, to a lesser extent, hypoalbuminemia may be indicators of esophageal varices in children. A clinical prediction rule using platelet count, spleen size z-score, and albumin level has been proposed to predict the presence of esophageal varices in children. Another index, the Brisk index, uses platelet count and bilirubin [14]. At present, however, no definitive prognostic model has been established as a standard predictor of esophageal varices in children. Splenomegaly, thrombocytopenia, and signs of liver failure inform the clinician that there is an increased risk of esophageal varices and bleeding.

The author of this study has mixed feelings about variceal prediction scales. It is difficult to be critical of predictions based on platelet counts and albumin levels when they are significantly low in children with decompensated cirrhosis caused by biliary atresia. Given the rate of progression of varices observed in children with CPH in the study group, despite the feasibility of screening endoscopy in children to detect varices remaining open [22], the author is inclined that mandatory screening endoscopy is obligatory, even in cases where the initial examination did not reveal varices.

Because endoscopic band ligation has fewer local complications than sclerotherapy, its use for primary prophylaxis has been extensively studied. Patients undergoing prophylactic endoscopic band ligation with Child-Turcotte-Pugh class B cirrhosis and high-risk varices had a significantly lower risk of bleeding than untreated patients. In addition, a trend toward reduced mortality and a reduction in blood transfusion requirements were observed in patients undergoing banding, which is very useful in the pretransplant course, as blood transfusion itself is considered an adverse immunological event [4,22]. In the studied group, band ligation procedure allowed for the reduction of the degree of varicose veins, reducing it to grade I in 5 (25.0%) patients ($p<0.001$), while complete eradication was not achieved in any of the patients.

Recurrence of varices of the esophagus is reported in the pediatric literature with a frequency of 10–40% of cases after the use of sclerotherapy as secondary prevention. Studies report a rapid recurrence of high-grade varices of the esophagus, with recent studies [12] showing a higher rate of recurrent bleeding than was described in previous studies. This difference may reflect the fact that the sclerotherapy group had a younger

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mean age than in the aforementioned studies, and ligation was not possible in this group of patients because the ligation device could not pass through the patient's pharynx [10,12,17]. Younger age may contribute to an increased incidence of rebleeding. The same was observed in the study group, where the endoscopic sclerotherapy was applied to patients with biliary atresia, too small to pass the ligation device. Sclerotherapy is performed every 10 to 14 days until variceal eradication, which usually requires repetitive sessions, up to 6 in adults. Each session can cause local or systemic complications. Superficial ulcers are the most common complication (70% at 1 week). Endoscopic sclerotherapy reduces the risk of recurrent esophageal variceal bleeding from approximately 65% to 30% at 1 year, but does not reduce overall mortality. After variceal obliteration, varices tend to recur over time in 50 to 70% of patients [4]. In the studied patients, no complications were observed.

Conclusions

Endoscopic methods of variceal bleeding prophylaxis and management are widely used to control acute recurrent bleeding, which is caused by the progression of the underlying ESLD and CPH, respectively, which might provide the prophylaxis of the deterioration of patients' condition in the pretransplant period, and influence the improvement of liver transplantation outcome. Endoscopic band ligation allowed for the reduction of the varices grade to grade I ($p<0.001$) in a small number of patients in the prospective study group. Endoscopic sclerotherapy in patients with CPH did not significantly affect the number of patients with high-grade esophageal varices ($p=0.815$ and $p=0.701$, respectively), mostly due to the progression of underlying ESLD. Mandatory screening endoscopy is obligatory in children with CPH, especially those who are listed for liver transplantation.

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