Analysis of the effectiveness of the method of primary bleeding prevention in the treatment of portal hypertension in children

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Abstract

Objective. To evaluate the role of primary prevention of variceal bleeding in children with prehepatic portal vein obstruction.

Materials and methods. The single–centre prospective cohort clinical trial involved 120 patients with extrahepatic obstruction of the hepatic portal vein who underwent primary or secondary prevention of variceal bleeding in 2016–2021. Laboratory, ultrasound, and endoscopic data were collected and evaluated before and after prophylactic treatment.

Results. Episodes of variceal bleeding were observed in 3 (5.78%) patients who received primary prophylaxis, and rebleeding occurred in 19 (27.94%) patients who received secondary prophylaxis (p=0.013). Of the 53 (44.17%) patients who underwent endoscopic treatment, variceal bleeding occurred in 3 (5.66%), and 19 (28.36%) of the 67 (55.83%) patients who underwent surgery experienced rebleeding (p=0.001). Esophageal varices eradication was achieved in 83 (69.17%) patients: 44 (53.01%) patients who received primary prevention and 39 (46.99%) patients who received secondary prevention. Bleeding episodes occurred less frequently after eradication (p<0.001). After primary prevention, varicose veins disappeared more often than after secondary prevention (p=0.005). The incidence of varicose veins recurrence after achieving eradication did not differ in the groups (p=0.51).

Conclusions. Primary prevention can reduce the high risk of bleeding in prehepatic portal vein obstruction. Prophylactic endoscopic ligation is important in the treatment of portal hypertension in children, which, together with portosystemic shunting, can potentially improve the results of preventive treatment.

Key words: children; portal hypertension; liver; hepatocytes; bleeding; shunting.

Portal vein obstruction (PVO) is a vascular lesion of the liver, the most common cause of portal hypertension (PH) in children [1, 2]. Thrombosis of the portal vein with subsequent cavernous formation causes direct injury to the portal vein and its branches, while in other observations, the prehepatic form of PH is considered idiopathic. Umbilical vein catheterisation is the main cause of PH in developing countries, while it is extremely rare in high–income countries [3].

Bleeding from varicose veins is a life–threatening complication of PG in children, which can lead to increased morbidity and mortality, despite the use of modern surgical and endoscopic methods of haemostasis [4].

According to global recommendations, secondary prevention of PG should always be carried out in children [5]. However, research is still ongoing to determine its optimal method and stages. Meso–portal shunting is chosen as a method of surgical treatment of PG in children [6], but it is associated with such limitations as the presence of favourable anatomy of the intrahepatic part of the portal bed and surgeon's experience. The widespread use of surgical methods for the treatment of PH in children and the results of relevant long–term studies have formed an understanding of the causes and consequences of changes in portohepatic perfusion in these patients [7].

Esophagogastroduodenoscopy is considered a standard diagnostic and therapeutic procedure for the detection and monitoring of esophageal and gastric varices with the possibility of early endoscopic eradication [8]. Endoscopic ligation (EL) and sclerotherapy are equally effective methods of bleeding prevention.

The aim of the study was to evaluate the role of primary prevention of variceal bleeding in children with prehepatic venous insufficiency.

Materials and methods

A single–centre prospective cohort clinical trial was conducted involving 120 patients with PG who received primary or secondary prophylaxis of HBV in the Emergency Surgery Department and Endoscopy Department of the National Children's Specialised Hospital "Okhmatdyt" of the Ministry of Health of Ukraine in 2016–2021. The Clinical Trials Committee of the Bogomolets National Medical University approved this study (minutes of the committee meeting No. 141 of 27.01.2021). All studies were conducted in accordance with the implemented guidelines in compliance...
with the rules of good clinical practice (GCP–ICH) and the Declaration of Helsinki [9]. The results of the study are part of the research work of the Bogomolets National Medical University (No 0122U001363), which is funded by the Ministry of Health of Ukraine from the state budget. Written informed consent was obtained from all parents/guardians of the study participants.

The OVPV was confirmed by ultrasound examination with Doppler of the portal system vessels and multislice computed tomography of the abdominal cavity with intravenous contrast. Endoscopic and laboratory data (complete blood count with platelet count, biochemical screening of liver function) were collected immediately before the start of prophylactic treatment and in the future.

Depending on the type of prophylaxis, patients (n = 120) were divided into two groups. Group 1 (primary prevention) included 52 (43.33%) patients who underwent EL or various variants of portosystemic bypass (PSB) to prevent the first episode of varicose vein bleeding, and group 2 (secondary prevention) included 68 (56.67%) patients who underwent EL or PSB to prevent recurrence after stopping the first varicose vein bleeding.

Variables and definitions under study:

- Esophageal EBV with a high risk of bleeding was defined as grade III esophageal EBV according to the Second Edition Esophageal Varices Classification of the Japanese Society for Gastrointestinal Research [10] or grade II in combination with gastric EBV grade GOV1 or GOV2 according to the classification of S. K. Sarin and A. Kumar [11] and/or the presence of red "signs" [12];
- recurrent bleeding episodes are defined as bleeding from varicose veins after the start of prophylaxis (primary or secondary), requiring blood transfusion, Black–Moore probe placement, urgent endoscopy or surgery;
- recurrence of oesophageal CRC is defined as the reappearance of oesophageal CRC after eradication has been achieved; esophageal CRV was considered to be eliminated by its disappearance or reduction of manifestations to grade I;
- thrombocytopenia was classified according to the control platelet count as mild (<150 $\times$ 10$^9$/l), moderate (<100 $\times$ 10$^9$/l) and severe (<50 $\times$ 10$^9$/l) [13].

**Statistical analysis.** Data were analysed using EZR Statistical Software v.1.6 (R Foundation for Statistical Computing). Categorical variables were compared using Fisher's exact

### Characteristics of the study groups according to primary clinical, laboratory and endoscopic data

<table>
<thead>
<tr>
<th>Variable value</th>
<th>1st (primary prevention), n=52</th>
<th>2nd (secondary prevention), n=68</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
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<td></td>
<td></td>
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<tr>
<td>ч</td>
<td>33 (63.46)</td>
<td>46 (67.65)</td>
<td>0.777*</td>
</tr>
<tr>
<td>ж</td>
<td>19 (36.54)</td>
<td>22 (32.35)</td>
<td></td>
</tr>
<tr>
<td>Age, years (x ± SD)</td>
<td>6.78± 0.63</td>
<td>6.38± 0.501</td>
<td>0.611*</td>
</tr>
<tr>
<td>Platelets, $\times$ 10$^9$/l (x± SD)</td>
<td>109± 6.66</td>
<td>138.2± 11.92</td>
<td>0.043*</td>
</tr>
<tr>
<td>White blood cells, $\times$ 10$^9$/l (median (Q1+Q3))</td>
<td>4.2 (3.09+5.01)</td>
<td>3.5 (2.8+5.50)</td>
<td>0.233**</td>
</tr>
<tr>
<td>Spleen volume, cm$^3$ (median (Q1+Q3))</td>
<td>335 (226+477)</td>
<td>326 (204+500)</td>
<td>0.76**</td>
</tr>
<tr>
<td>Oesophageal ERV, n (%)</td>
<td>38 (73.08)</td>
<td>30 (44.12)</td>
<td>0.003*</td>
</tr>
<tr>
<td>II degree</td>
<td>14 (26.92)</td>
<td>38 (55.88)</td>
<td></td>
</tr>
<tr>
<td>III degree</td>
<td>50 (96.15)</td>
<td>64 (94.12)</td>
<td>0.934*</td>
</tr>
<tr>
<td>yes</td>
<td>2 (3.85)</td>
<td>4 (5.88)</td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>16 (30.77)</td>
<td>10 (14.71)</td>
<td></td>
</tr>
<tr>
<td>Red &quot;signs&quot;, n (%)</td>
<td>36 (69.23)</td>
<td>58 (85.29)</td>
<td>0.058*</td>
</tr>
<tr>
<td>yes</td>
<td>44 (84.62)</td>
<td>61 (89.71)</td>
<td>0.31*</td>
</tr>
<tr>
<td>no</td>
<td>8 (15.38)</td>
<td>7 (10.29)</td>
<td>0.093*</td>
</tr>
<tr>
<td>Portal gastropathy, n (%)</td>
<td>28 (53.85)</td>
<td>25 (36.76)</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>24 (46.15)</td>
<td>43 (63.24)</td>
<td></td>
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<tr>
<td>no</td>
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</tbody>
</table>

**Note.** * - χ$^2$ test;* - Student's test; ** - Wilcoxon test.
test; continuous variables with a normal distribution were compared using Student's T–test; continuous variables with a non–normal distribution were compared using Wilcoxon's W–test. The significance level was set at less than 0.05 (p<0.05). To identify the factors associated with the occurrence of bleeding from varicose veins and with the achievement of eradication, a multivariate analysis was performed with the construction of a logistic regression model. Survival rates without episodes of recurrent bleeding were analysed using the Kaplan–Meier method.

**Results**

The study cohort included 79 (65.83%) boys and 41 (34.17%) girls. The mean age of patients at the time of starting prophylactic treatment was 6 years (Q1–Q3: 3–9.5). Initial manifestations of PG were bleeding from varicose veins in 47 (39.17%) children, splenomegaly in 32 (26.67%), abdominal enlargement in 18 (15%), anaemia in 7 (5.83%), thrombocytopenia in 5 (4.17%), hepatosplenomegaly in 5 (4.17%), and abdominal pain in 5 (4.17%). In 1 (0.83%) patient, computed tomography revealed an incidental IAA aneurysm.

The main causes of PH were idiopathic cavernous transformation of the IVC in 41 (34.17%) patients and IVC thrombosis in 79 (65.83%) patients. Umbilical vein catheterisation in the postnatal period was noted in 69 (87.34%) patients, omphalitis in 2 (2.53%), confirmed thrombophilia in 4 (5.06%), and postoperative IVC thrombosis in 4 (5.06%).

When comparing the study groups (see Table) according to the primary clinical, laboratory and endoscopic data using the chi–square and Student's T–test, no homogeneity was found (p>0.05) in terms of the number of patients with grade II and III esophageal CRV (chi–square = 8.92, p = 0.003) and platelet count (Student's T–test = 2.07, p = 0.043). However, all study patients had a high risk of bleeding according to endoscopic findings. Thus, the difference in these indicators between the groups could not distort the results of the study.

In order to find out which factors may indicate the occurrence of bleeding from varicose veins, a logistic regression model was analysed and an ROC curve was constructed (Fig. 1). It was found that only one factor influenced the occurrence of bleeding. Thus, with the progression of the degree of varicose veins, the risk of bleeding before prophylactic treatment increases: odds ratio = 3.37 (95% confidence interval 1.46 – 7.78), p = 0.004.

Bleeding episodes occurred in 3 (5.77%) patients in group 1 (primary prevention), and repeated bleeding occurred in 19 (27.94%) patients in group 2 (secondary prevention) after treatment.

When comparing the frequency of recurrent bleeding after prophylactic treatment in the study groups, it was found that in patients in group 1 (primary prevention), recurrent bleeding occurred less frequently (chi–square = 6.1, p = 0.013 by the Kaplan–Meier method). The median survival rate without recurrent bleeding (Fig. 2) in group 1 (primary prevention) was not achieved during the 52–month follow–up period, in group 2 (secondary prevention) it was 60 months (41 – ∞). It was found that primary prevention could reduce (p=0.001 by Fisher's exact test) the likelihood of variceal bleeding compared with secondary prevention: odds ratio = 0.16 (95% confidence interval 0.03%–0.59%). Of the
53 (44.17%) patients who received endoscopic treatment, 3 (5.66%) experienced rebleeding, and of the 67 (55.83%) patients who received surgical treatment alone, 19 (28.36%) experienced rebleeding (p=0.001 by Fisher's exact test). In group 1, none of the 28 patients who underwent EL vein treatment experienced recurrent bleeding, and of the 24 patients who underwent PCI, 3 (12.5%) experienced recurrent bleeding. In group 2, 3 (12%) of 25 patients undergoing EL vein therapy experienced recurrent bleeding, and 16 (37.21%) of 43 patients undergoing PCI. There was no statistically significant difference between the incidence of rebleeding from varicose veins in group 1 (primary prevention) and group 2 (secondary prevention): chi–square=1.77, p=0.18 and chi–square=3.82, p=0.051, respectively.

Eradication of varicose veins was achieved in 83 (69.17%) patients: 44 (53.01%) in group 1 (primary prevention) and 39 (46.99%) in group 2 (secondary prevention). After primary prevention, varicose veins disappeared more often than after secondary prevention (chi–square=9.03, p=0.003).

Among the 83 (69.17%) patients who achieved varicose vein eradication, 4 (3.33%) had recurrent bleeding: 1 (25%) due to portal hypertensive gastropathy, 1 (25%) due to gastric varices, and 2 (50%) due to recurrence of esophageal varices. Among the 37 (30.83%) patients who did not achieve varicose vein eradication, 18 (15%) had recurrent bleeding. It was found that after achieving eradication, recurrent bleeding occurred less frequently (p<0.001 by Fisher's exact test).

After endoscopic treatment, varicose vein eradication was achieved more often – in 50 (94.33%) out of 53 (44.17%) patients than after surgical treatment – in 33 (49.25%) out of 67 (55.83%) patients (p<0.001 by Fisher's exact test). In particular, in group 1, eradication was not achieved in only 1 (3.57%) of 28 patients who underwent EL vein therapy and in 7 (29.17%) of 24 patients who underwent PSA. In group 2, eradication was not achieved in 2 (8%) of 25 patients who underwent EL vein and in 26 (60.47%) of 43 patients who underwent PSH. A statistically significant difference was found between the rates of eradication after EL vein and PSA in group 1 (primary prevention) and group 2 (secondary prevention): chi–square=4.69, p=0.03 and chi–square=15.86, p<0.001, respectively.

To identify factors that impede the achievement of varicose vein eradication, a logistic regression model was analysed and an ROC curve was constructed (Fig. 3). It was found that the presence of bleeding from varicose veins before the start of secondary prevention (odds ratio = 0.28 (95% confidence interval 0.11 – 0.77), p<0.001) and PSA (odds ratio 0.33 (95% confidence interval 0.12 – 0.93), p=0.036) reduced the chances of achieving eradication. Thus, primary prevention and the choice of the EL vein method could increase the frequency of achieving eradication.

After achieving eradication, varicose veins recurred in 10 (12.05%) patients: 4 (40%) who underwent primary prevention and 6 (60%) who underwent secondary prevention. In terms of the number of episodes of varicose veins recurrence, there were no statistically significant differences between the groups (p=0.51). In group 1, varicose veins recurred in 3 (11.11%) of 27 patients who underwent EL veins and in 1 (5.88%) of 17 patients who underwent PSV. In group 2, varicose veins recurred in 3 (13.04%) of 23 patients who underwent EL vein and in 3 (17.65%) of 17 patients who underwent PSH. There was no statistically significant difference between these indicators according to the chi–square criterion for both groups: chi–square=0.00, p=0.962 – group 1, chi–square=0.00, p=0.965 – group 2.

Discussion
There is no consensus on the need for primary prevention of variceal bleeding in children with PH [6], although it is widely used in adults. However, an episode of bleeding from varicose veins always has severe psychological consequences for both the child and his or her parents, especially when hematemesis occurs [14]. In addition, in developing countries, emergency endoscopic or surgical treatment of bleeding is mostly available only in tertiary care centres [15]. OOPV causes up to 80% of bleeding episodes from the upper digestive tract in children due to ruptured esophageal and gastric varices [3, 4]. Oesophageal varices are present in 90–95% of patients with PG [16]. The morbidity and mortality rates of bleeding from varicose veins are high. A mortality rate of 19% has been reported within 35 days after the onset of bleeding in children with chronic liver disease [17]. Therefore, it is unreasonable to underestimate the importance of
preventing bleeding from varicose veins in children with PG.

Primary prevention requires the identification of endoscopic signs of varices with a high risk of bleeding [18]. In 96% of children with various etiologies of PH and spontaneous bleeding episodes, grade II or III esophageal varices with red spots on endoscopy and/or gastric varices extending to the cardiac system were present [18]. The presence of medium and large esophageal varices increases the risk of bleeding in children with OOPV with PH [19]. According to our data, the progression of varicose veins increases the risk of bleeding from varicose veins in children with PH. Despite the fact that in the vast majority of studies in patients with PG, the presence of gastric varicose veins is considered as one of the risk factors for bleeding [18, 20], according to the results of our study, this factor did not affect the risk of bleeding from varicose veins.

Although there is no consensus on the use of primary prevention of variceal bleeding, various researchers believe that prophylactic treatment of varicose veins with a high risk of bleeding can potentially improve the treatment strategy and quality of life of patients with PG of various etiologies [18, 21–25]. Out of 28 medical centres, 20 used treatment by primary prevention of bleeding from varicose veins, one centre used it only for patients with cystic fibrosis, and the rest referred their patients to tertiary care centres as needed [26]. Primary prevention should be implemented if there are endoscopic signs of risk of bleeding from varicose veins [20]. The chances of 10–year bleeding–free survival after successful primary prevention were 96% for patients with prehepatic varices and 72% for patients with cirrhotic varices [18]. Our study has shown that the use of primary prophylaxis can reduce the likelihood of variceal bleeding in patients with PAP. Rebleeding occurred in 5.77% of patients treated with primary prevention and in 27.94% of patients treated with secondary prevention.

According to our data, episodes of recurrent bleeding were less frequent when varices were eradicated. Both primary and secondary prevention were associated with high rates of esophageal varices eradication, although the recurrence rate was also significant [19]. In our study, varicose veins recurrence was detected in 12.05% of patients. According to this indicator, there was no statistically significant difference between group 1 (primary prevention) and group 2 (secondary prevention).

According to the literature, the frequency of rebleeding ranges from 24 to 42% in patients undergoing PCI [27, 28]. At the same time, patients who underwent EL of veins had less frequent rebleeding and achieved faster eradication [21, 29–31]. The analysis of our data showed that primary prevention and the use of EL veins increased the frequency of achieving eradication. This can be explained by the direct effect of EL veins on varicose veins. EL veins do not affect the pressure in the portal system, so they cannot be a radical treatment for the prehepatic form of PG. In case of hypersplenism and splenomegaly, sooner or later the question of shunting, in particular meso–portal shunting, will arise. When meso–portal shunting is not possible, vein elastography can be an effective and affordable alternative option for the primary or secondary prevention of bleeding from varicose veins.

**Conclusions**

The degree of progression of the VWD may increase the risk of bleeding in children with ARVC. Primary prophylaxis should be used in children with PG and a high risk of bleeding, as it can reduce the chances of bleeding. According to the Kaplan–Meier estimates, primary prevention is more effective than secondary prevention (median survival for primary prevention was not achieved during the 52–month follow–up period). The use of EL veins remains controversial, as this method is temporary, does not affect pathophysiological vascular branches and does not eliminate the possible cause of bleeding in PG. At the same time, endoscopic prophylaxis is an important component in the treatment of paediatric patients with PG. Vein EL can be an effective and affordable alternative option for the primary or secondary prevention of bleeding from varicose veins, which allows achieving varicose vein eradication more often than PSE.

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**References**


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