



Submitted on: 06/02/2024

Approved on: 09/16/2024

REVIEW ARTICLE

Primary prophylaxis of variceal upper gastrointestinal bleeding in children and adolescents with portal hypertension: an integrative review

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Keywords:

Liver cirrhosis,
Esophageal and
gastric varices,
Child,
Adolescent,
Propranolol,
Endoscopy,
Gastrointestinal

Abstract

Portal hypertension is characterized by increased blood pressure in the portal vein and its branches. Recent studies indicate that upper gastrointestinal bleeding in children is associated with significant morbidity, although mortality rates are lower than in adults. Prophylactic strategies are implemented in some pediatric centers, but there is no consensus on the optimal management for this population. The aim of this study was to conduct an integrative review on the primary prophylaxis of variceal UGIB in the pediatric population with portal hypertension, whether cirrhotic or not, through the use of beta-blockers and endoscopic procedures such as elastic band ligation and sclerotherapy. A integrative review of the scientific literature was conducted on the PubMed/Medline databases. A total of 153 articles were identified, and 26 were selected for integrative review after a thorough examination, comprising 2 meta-analyses, 3 randomized clinical trials, and 21 uncontrolled observational studies. The integrative review highlight the challenges and limitations associated with the use of non-selective beta-blockers in children, revealing a considerable frequency of side effects leading to drug discontinuation. Comparative studies indicate a higher risk of bleeding in the group using propranolol compared to primary endoscopic prophylaxis, despite methodological limitations. As for the evaluated studies on primary endoscopic prophylaxis, they suggest few complications and demonstrate efficacy in variceal eradication, although a high risk of recurrence persists.

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INTRODUCTION

Upper gastrointestinal bleeding (UGIB) secondary to ruptured esophageal varices (EVs) is one of the most common complications of portal hypertension and the leading cause of morbidity and mortality in adults with chronic liver disease. Therefore, strategies aimed at reducing portal pressure and consequently preventing UGIB, among other complications, are highly desirable¹.

To this end, the Baveno Committee has periodically convened experts since 1990 to develop guidelines based on the best available scientific evidence for the management of portal hypertension, including the management of acute variceal bleeding and primary and secondary prophylaxis of UGIB. In these initial documents, endoscopic screening for the presence of EV was recommended for all patients with cirrhosis at the time of diagnosis. For patients with medium- or large-caliber EVs and no previous history of UGIB, primary prophylaxis with a nonselective beta-blocker or endoscopic ligation was indicated. These early guidelines did not contain specific recommendations for children²⁻⁵.

In 2005, a panel of experts was convened to review and adapt the Baveno IV report for the pediatric population. In this document, due to the lack of robust scientific evidence, primary prophylaxis in the pediatric age group was not recommended for all children with portal hypertension at risk of bleeding, but only within research protocols⁶. In Baveno V, this recommendation was maintained with an individualized assessment of each case, considering children at higher risk of mortality from UGIB, such as those not within reasonable proximity to medical care⁷.

In 2015, Baveno VI held a satellite symposium focusing on the pediatric population, published in 2016. However, this publication was limited to discussing the available evidence on the indications for the *shunt*. Mesorex in extrahepatic portal vein obstruction (EHVPO). Again, there was no consensus regarding primary prophylaxis of EV in cirrhotic patients due to the lack of evidence in the age group⁸.

The last meeting, Baveno VII, was in October 2021. In adult patients, Baveno VII recommends the use of elastography for the early identification of patients with chronic liver disease at risk of developing clinically significant portal hypertension. This consensus statement focuses not on EV screening nor solely on primary prophylaxis of UGIB, but on the prevention of decompensation in general. Transient hepatic elastography ≤ 15 kPa associated with a platelet count $\geq 150,000$ rules out clinically significant portal hypertension in patients with clinically significant liver disease (sensitivity and negative predictive value $>90\%$). For patients with clinically significant portal hypertension, the use of nonselective beta-blockers (propranolol, nadolol, or carvedilol) is indicated to prevent decompensation, with carvedilol being the first choice. Once on beta-blockers, patients do not require endoscopic screening, as this will not change their management.

Endoscopy is only indicated for those with contraindications or adverse effects associated with beta-blocker use; in patients with high-risk varices and contraindications or intolerance to beta-blockers, esophageal variceal band ligation (EVL) should be recommended. This consensus statement did not provide any specific recommendations for the pediatric population, again due to the lack of studies in this age group⁹. The use of liver elastography has been increasingly recommended as a noninvasive measure of prognosis in adults. It is important to consider that in the pediatric population, elastography values are not yet well established¹⁰.

In children, beta-blockers have already been used as primary prevention of UGIB; however, there are few studies with results showing a higher bleeding rate compared to primary endoscopic prophylaxis¹¹.

We currently know that UGIB episodes are associated with high morbidity and increased mortality, although at lower rates compared to adults^{12,13}. A retrospective study evaluated morbidity and mortality in 174 UGIB episodes in children with portal hypertension within 6 weeks of bleeding. Ascites was the most common complication (43.1%), being more prevalent in patients with cirrhosis. In addition, other complications described were infection (31%), encephalopathy (14.9%), and the need for invasive ventilation (12.6%). There were no deaths from UGIB in the 6 weeks after bleeding, but morbidity was significant¹⁴.

On the other hand, a longitudinal, multicenter study published in 2022 analyzed 869 children with biliary atresia from 16 centers in the United States and Canada over a 16-year period. The median age at portoenterostomy was 60 days of life. The overall incidence of first-episode UGIB in the 5-year follow-up was 9.4% (95% CI: 7-12.4) in the prospective study. In patients with signs of portal hypertension (splenomegaly and/or thrombocytopenia), the incidence rose to 21.7% (95% CI: 9.1-37.7). Five-year survival with native liver transplantation was 45.1%¹⁵. The authors consider the risk of UGIB to be low, but it is important to contextualize the reality in the United States, with a median age at portoenterostomy of 60 days and almost half of transplant patients before 5 years of age. This fact changes the prognosis for patients, but it is not yet a reality in many developing countries, including Brazil. On the other hand, morbidity is high, and all these factors must be considered when deciding whether or not to implement prophylactic measures.

Although there is no explicit recommendation for screening and primary prophylaxis in children with portal hypertension, a 2011 study administered questionnaires to Canadian pediatric gastroenterologists and hepatologists. As a result, 70% of respondents reported screening for EV in selected children, and 58% performed primary prophylactic treatment¹⁶. In a 2017 study of professionals from 38 French-speaking hospitals, more than 75% reported using endoscopy to screen patients with suspected portal hypertension, and more than 90% reported performing sclerotherapy or EVS

when grade 2 varices with red spots and grade 3 varices were detected. Nonselective beta-blockers were used by approximately 20% of the centers interviewed¹⁷.

Thus, the topic is controversial and the objective of this work was to carry out an integrative review on the primary prophylaxis of varicose UGIB in the pediatric population with portal hypertension, cirrhotic or not, with beta-blockers or endoscopic procedures, such as LEVE and sclerotherapy.

METHODOLOGY

An integrative review of the scientific literature was carried out in the PUBMED/MEDLINE databases using the English terms “Endoscopic variceal ligation”, “High-risk varices”, “Endoscopic management”, “Gastrointestinal bleeding”, “Portal hypertension”, “Esophageal varices”, “Ligation”, “Banding”, “Prophylaxis”, “Prevention”, “Children”, “Infants” and “Adolescents”. Articles in English and Portuguese, without date restrictions, with patients aged between 0 and 18 years were evaluated.

RESULTS

A total of 153 articles were identified through a PUBMED search. After a complete reading, 26 were selected for integrative review: 2 meta-analyses, 3 randomized clinical trials, and 21 uncontrolled observational trials.

Use of Beta Blockers

Non-selective beta-blockers are the mainstay for the treatment of portal hypertension in adults with liver cirrhosis^{9,18}.

Non-selective beta-blockers act on both beta-1 and beta-2 adrenergic receptors. Beta-1 blockade reduces heart rate and cardiac output, with a decrease in blood flow of approximately 20%. Beta-2 blockade causes splanchnic vasoconstriction due to unopposed adrenergic tone, resulting in a reduction in portal blood flow. Carvedilol is a non-selective beta-blocker with an intrinsic anti-alpha-1 adrenergic effect, causing intrahepatic vasodilation and further decreasing portal pressure. Studies in adult populations have shown that carvedilol was better tolerated than therapeutic doses of propranolol¹⁸.

Through these mechanisms, nonselective beta-blockers reduce portal pressure by approximately 15%. Randomized clinical trials demonstrate their efficacy in preventing initial variceal bleeding and subsequent rebleeding. Recent evidence also indicates that beta-blockers can prevent hepatic decompensation in patients with compensated cirrhosis and the risk of death^{9,18-20}.

Unlike the evidence in the adult population, studies in the pediatric population are quite limited. A Cochrane review on the topic was published in 2021, but no randomized clinical trials were found for analysis comparing beta-blocker use with

no intervention²¹. One randomized clinical trial was excluded from the analysis because children were randomized to two groups with different beta-blockers (propranolol and carvedilol) without a control group²². Most studies conducted to date are observational and retrospective and will be detailed below (TABLE 1).

The first study on propranolol in portal hypertension in children was published in 1985 by Ozsoylu *et al.* to evaluate portal pressure²³. Thirteen children with portal hypertension were administered propranolol (initial dose of 2 mg/kg/day and maximum of 8 mg/kg/day) until a 25% reduction in heart rate was achieved. Portal pressure (measured by splenic pressure) was reduced in all patients with compensated portal hypertension and in only 3 of the 8 with decompensated portal hypertension. No distinction was made between primary and secondary prophylaxis, nor was there long-term follow-up to assess the risk of UGIB²³.

Between 1989 and 1996, Shashidhar *et al.*²⁴ retrospectively evaluated 21 children who received only propranolol as primary prophylaxis (17 patients) and secondary prophylaxis (4 patients), with ages ranging from 9 months to 18 years. Of the selected patients, 19 (90.4%) had portal hypertension secondary to cirrhosis (8 patients with biliary atresia) and two (9.5%) due to EHPVO. The grading of VE was described in 16 patients: 11 (68%) with small caliber and 5 (31%) with large caliber. The dose of propranolol was adjusted until a 25% reduction in resting heart rate was achieved: ten patients (47.6%) received doses between 1.0 and 2.0 mg/kg/day, six (28.5%) received doses lower than 1 mg/kg/day, and five (23.8%) were receiving doses higher than 2.0 mg/kg/day. The desired reduction in heart rate was achieved in 17 (80.9%) patients. During the follow-up period (mean 30 months), fourteen (66.6%) of the 21 patients did not experience UGIB. Of the seven patients who had bleeding episodes (six on primary prophylaxis and one on secondary prophylaxis), two (28.5%) did not adhere well to the medication, and four (57.1%) were receiving doses lower than 1 mg/kg/day. Two of the three patients who had a heart rate reduction of less than 25% experienced UGIB. Side effects were minimal: two patients reported dizziness and headache. No patient in the study required discontinuation of therapy. The main limitations of this study are the fact that most patients had small-caliber LV (known to have a lower risk of bleeding) and the lack of stratification according to the severity of liver disease²⁴.

In 2003, Erkan *et al.*²⁵ retrospectively and descriptively evaluated 62 children with portal hypertension (16 with extrahepatic causes and 46 with intrahepatic causes) who received primary (22 patients) or secondary (40 patients) prophylaxis. The choice of treatment type depended on the degree of LV found: patients with small- or medium-caliber varices were treated with propranolol monotherapy, and patients with large-caliber varices randomly received sclerotherapy alone or combined treatment. The dose of propranolol used was 1 to 2 mg/kg/day, adjusted until a

Table 1. Studies on propranolol and other beta-blockers in the primary prophylaxis of variceal gastrointestinal bleeding in children and adolescents.

Study	Design and Prophylaxis	N	Outcome	Main Results	Follow-up Time	Observations
Ozsoylu <i>et al.</i> (1985) ²³ Türkiye	Case series Retrospective Propranolol	13 prophylaxis 1 st and 2 nd	Portal pressure, measured in the splenic vein	Reduction in splenic pressure in all compensated patients and only in 3/8 with decompensated symptoms	Not informed	Does not report HDA outcome, nor distinction between 1 st and 2 nd prophylaxis
Shashidar <i>et al.</i> (1999) ²⁴ USA	Case series Retrospective Propranolol	17 prophylaxis 1 st	HDA	HDA: 6/17 (35.3%), related to adherence or non-response. No patient in the study needed to discontinue therapy due to side effects.	Average 30 months	Limitations: most patients with small caliber LV (known to have a lower risk of bleeding), lack of stratification according to severity
Erkan <i>et al.</i> (2003) ²⁵ Türkiye	Retrospective case series	22 prophylaxis 1 st 13 only propranolol, 2 ET, 7 propranolol + ET	HDA	HDA: Propranolol group: 2/13 (15.4%) Combination therapy: 1/7 (14.3%).	5.2 ± 2.5 anos (minimum 2 years)	Propranolol and sclerotherapy were evaluated together
Samantha <i>et al.</i> (2011) ²² India	Randomized clinical trial Propranolol vs. carvedilol	Total 62 (41 sinusoidal portal hypertension and 21 pre-sinusoidal)	Efficacy defined as absence of HDA + reduction in the degree of VE, VG or gastropathy of portal hypertension	Decrease in VE degree: 40/62 (64.5%) Increased degree of VE: 9/62 (14.5%) 8/9 children with associated VGE, the severity of the injuries reduced. Carvedilol was more effective than propranolol at months 4 and 5 of follow-up (p = 0.035 and 0.034), but with similar long-term results.	2 years	Presinusoidal etiology responded better to treatment, both propranolol and carvedilol . Limitations: most patients had a smaller caliber LV, i.e., a low risk of bleeding
Pimenta <i>et al.</i> (2016) ²⁶ Brazil	Retrospective case series Propranolol X Mild	26 cirrhotics 17 propranolol 13 LIGHT: 9 contraindications + 4 side effects of propranolol	HDA	HDA in the propranolol group: 6/17 (35.6%) - 3 (17.6%) died due to HDA. 7/17 (41.2%) propranolol was suspended, 3 due to beta-blockade failure and 4 due to adverse effects such as drowsiness, bronchospasm and hypotension.	Propranolol 2.7 years (1.2-3.5) LIGHT 2.2 years (1.9-2.6)	In the group of patients who underwent primary endoscopic prophylaxis with LEVE, no episodes of UGIB were observed.
Quintero <i>et al.</i> (2020) ¹¹ Spain	Cohort Retrospective Propranolol vs. Prospective LEVE	Total 64 – 32 in each group Propranolol retrospective control group	HDA	UGIB in the propranolol group 7/32 (21.9%) Risk of UGIB for propranolol X MILD 2.6 (95% CI, 1.53-3.67)	Minimum of 1 year	There was no significant difference observed in survival at 1 and 3 years of follow-up between the two groups.

ET: sclerotherapy; LEVE band ligation of esophageal varices; UGIB (upper gastrointestinal bleeding); HP (portal hypertension); EHVP (extrahepatic portal vein obstruction); VE (esophageal varices); VG (gastric varices).

25% reduction in heart rate was achieved. For primary prophylaxis, 13 patients received propranolol alone, 2 received sclerotherapy, and 7 received a combination of the two treatments. Two patients receiving propranolol bled during follow-up (15.4%), and one of the 7 patients receiving combined therapy bled (14.3%). Despite the limitations, including the joint evaluation of patients undergoing primary and secondary prophylaxis, the study had a long treatment follow-up period of 5.2 ± 2.5 years (minimum of 2 years)²⁵.

In 2011, Samanta *et al.*²⁶ evaluated 62 children with portal hypertension under 12 years of age in a randomized clinical trial: one group received primary prophylaxis with propranolol and the other with carvedilol (31 patients in each group). The initial dose of propranolol was 1 mg/kg/day and that of carvedilol was 0.3 mg/kg/day, with the doses titrated until a 25% reduction in heart rate was achieved. All patients underwent endoscopy, initially monthly for the first 6 months, spaced out to quarterly during a 2-year follow-up period. Efficacy was defined as the absence of UGIB associated with a reduction in the degree of LV, gastric varices, or gastropathy due to portal hypertension. During follow-up, 3 children (4.83%) experienced bleeding (one in the propranolol group and 2 in the carvedilol group). There was a decrease in the severity of esophageal varices in 40 children, an increase in 9, and no change in 13 cases. Of the 9 children with associated gastroesophageal varices, 8 had reduced lesion severity. There were no side effects related to medication use during follow-up. Children with presinusoidal etiology responded better and more quickly to treatment with both propranolol and carvedilol. Carvedilol was statistically more effective than propranolol at months 4 and 5 of follow-up ($p = 0.035$ and $p = 0.034$), but with similar long-term results, highlighting the better cost-effectiveness of propranolol²². Although this was a randomized study, it is important to emphasize that most patients had smaller LV caliber at the beginning of treatment: 38 patients with grade I LV, 18 with grade II, and only 6 with grade III, meaning they had a lower risk of bleeding. The main outcome observed was the reduction in varicose vein size and not the relevant outcome, which is bleeding.

Published in 2016, Pimenta *et al.*²⁶ evaluated, in a descriptive study, a cohort of 26 pediatric cirrhotic patients between 2004 and 2014 who underwent primary prophylaxis for UGIB, with biliary atresia and autoimmune hepatitis being the most prevalent diagnoses. The median follow-up time was 2.7 (1.2-3.5) years in the propranolol group and 2.2 (1.9-2.6) years in the ligation group. Primary prophylaxis was indicated for those patients who had medium- or large-caliber varices or red spots. Endoscopic prophylaxis with LEVE was performed in patients with contraindications to beta-blockers or in those who discontinued treatment due to adverse effects or poor adherence. The propranolol dose ranged from 1 mg/kg/day to 3.1 mg/kg/day, adjusted monthly until a 25% reduction in heart rate was achieved. LEVE was repeated every 3 weeks until varicose vein eradication. Of the 26 patients followed,

17 received propranolol as primary prophylaxis and 9 had contraindications to beta-blocker use and underwent primary endoscopic prophylaxis. Six (35.6%) of the 17 patients receiving propranolol developed UGIB after a median follow-up of 1.9 years, and 3 (17.6%) died due to the episode. Seven (41.2%) patients had propranolol discontinued during follow-up: three due to beta-blockade failure and four due to adverse effects such as somnolence, bronchospasm, and hypotension. In the group of patients who underwent primary endoscopic prophylaxis with LEVE, no episodes of UGIB were observed. Thus, in this study, all patients who had UGIB were in the propranolol group. Furthermore, propranolol had a high number of contraindications and side effects. On the other hand, endoscopic prophylaxis was not associated with any bleeding episodes²⁶.

Quintero *et al.*¹¹ evaluated the efficacy and safety of propranolol in a retrospective arm (2009-2013) compared with LEVE prospectively (2014-2018) in children with portal hypertension and LV, with a minimum follow-up time of 1 year. There was no difference between the two groups regarding sex, age, weight, etiology of portal hypertension, follow-up time, laboratory and endoscopic data. The initial dose in the propranolol group was 1 mg/kg/day every 8 hours, titrated until a 25% reduction in baseline heart rate was achieved, but without exceeding the maximum dose of 5 mg/kg/day. Patients were reassessed monthly until the desired heart rate reduction was achieved and every 3 to 6 months thereafter. In the group of patients receiving propranolol prophylaxis, 7 of 32 patients (21.9%) experienced UGIB (1 death), and 7 (21.9%) had to discontinue treatment due to side effects (3 due to hypotension and 4 due to bronchospasm). All but 1 of the 25 patients who were able to maintain propranolol achieved the desired baseline heart rate. The mean dose was 2.4 mg/kg/day (range, 1.4-3.2 mg/kg/day). The mean time from initiation of propranolol to bleeding was 32.5 months. In the LEVE group, only 1 patient experienced UGIB. More detailed data on LEVE will be presented in the endoscopic prophylaxis section. Statistically significant differences in the bleeding rate were observed between the propranolol and ligation groups (7/32 [21.9%] vs. 1/32 [3.2%], $p < 0.02$). The bleeding hazard ratio for patients receiving propranolol compared with those receiving ligation was 2.6 (95% CI, 1.53-3.67). There was no significant difference in survival at 1 and 3 years of follow-up between the two groups. A limitation of this article is the use of a retrospective control group; nine patients in the propranolol group required liver transplantation. Therefore, the pretreatment severity of this group could have been greater, partially explaining the higher bleeding rate¹¹.

As can be seen, there are few studies on the subject (TABLE 1), with a limited number of patients, most of them retrospective and with several methodological limitations.

Although non-selective beta-blockers are well-established in adults with cirrhosis, they face a number of challenges and limitations in children. In our integrative

review, we detected a considerable frequency of side effects that resulted in discontinuation of the medication, the main ones being bronchospasm and hypotension. Furthermore, there is concern that beta-blockade may affect children's response to potential UGIB, since in this age group, it is heart rate-dependent. Doses varied widely, and most studies used the dose necessary to achieve a 25% reduction in baseline heart rate. However, in pediatric consultations, assessing resting heart rate can be difficult, making dose adjustment even more challenging. Furthermore, dose adjustments are necessary with weight gain, while heart rate decreases with age. Other factors to consider are the prolonged treatment duration and the risk of bleeding with even temporary discontinuation of the medication. The few studies comparing beta-blockers and primary endoscopic prophylaxis, despite the methodological limitations already described, showed that the risk of bleeding was higher in the group using propranolol. Therefore, multicenter, randomized, prospective studies are needed to better establish the role of beta-blockers, including carvedilol, in portal hypertension in pediatric patients, since these drugs have been shown to be important in preventing not only UGIB but also decompensated cirrhosis in adults^{9,18}.

Endoscopic Treatment

The first endoscopic treatment of UGIB due to bleeding varices was performed with sclerotherapy. After demonstrating its efficacy in controlling UGIB, sclerotherapy was also evaluated for primary prophylaxis. In children, experience has accumulated over 30 years, and therefore, it is not uncommon for studies to evaluate primary and secondary prophylaxis together. Subsequently, with the use of LEVE and its positive results, the trend shifted to this method for varicose vein eradication due to the lower risk of complications. Currently, most services that perform endoscopic primary prophylaxis prefer LEVE and reserve sclerotherapy for cases where ligation is technically impossible, especially in young children.

Only two randomized, controlled studies on endoscopic primary prophylaxis have been published to date: a Brazilian study by the Children's Institute of the University of São Paulo group²⁷ (evaluated sclerotherapy) and another by the group involving King's London College Hospital²⁸ (LEVE). This English study was published as a pilot to assess the feasibility and safety of a randomized clinical trial. Children with large varicose veins were randomized to receive prophylactic LEVE (12 children) or to the control group (10 patients). All completed at least 6 months of follow-up. One of the twelve (8%) children in the primary prophylaxis group developed UGIB one week after LEVE. Three of the ten (30%) children in the control group developed UGIB. Mortality was 8% in the ligation group (but from a cause unrelated to the intervention) compared to 0% in the control group. The study was published only as an abstract, without reporting the age or diagnosis of the children included²⁸. There have been no subsequent publications from the group since this pilot study.

The Cochrane review included only this study, the only randomized clinical trial found that evaluated LEVE as primary prophylaxis compared to no intervention. The study was considered at high risk of bias, and the evidence to support any recommendations was considered very scarce²⁹.

The other randomized study published evaluated the use of sclerotherapy as primary prophylaxis. Gonçalves *et al.*²⁷ evaluated, between 1991 and 1998, in a controlled, prospective, and randomized study, 100 children with portal hypertension and LVH less than grade IV, aged 11 months to 13 years (median, 4.3 years). Most patients had biliary atresia (37/100), 20 patients had cryptogenic cirrhosis, 13 had autoimmune hepatitis, and 9 had EHPVO. Most patients were Child A (88/100) and only 1 was Child C. Half of them received sclerotherapy and half were in the control group (only regular clinical and endoscopic examinations). The follow-up time ranged from 18 months (minimum time after the end of sclerotherapy sessions) to 8 years (median, 36 months). The prophylaxis group received sclerotherapy every 21 days until complete variceal obliteration. The control group underwent endoscopies every six months. The most common complication observed was pain and fever after the procedure, which resolved with analgesia, without major complications. During this period, sclerotherapy eradicated EV in 47/50 children (94%), but only 38 of them (76%) did not develop UGIB. Before complete variceal eradication, UGIB occurred in 12 patients (24%). Six children (12%) had gastric varices, and 3 of them (50%) bled. During this period, 9 (18%) of the patients in the sclerotherapy group died: 3 of them from UGIB and the others from sepsis or end-stage liver disease. In the control group, 42% of the children had variceal bleeding. Eight children (16%) in the control group died (4 from UGIB and 4 from end-stage liver disease or sepsis). Endoscopic sclerotherapy reduced the risk of UGIB (24% vs. 48% - $p < 0.05$), but did not improve the mortality rate (18% vs. 16% - $p > 0.05$). Sclerotherapy did not increase the incidence of gastric varices ($p > 0.05$), but when present, there was a higher risk of bleeding (3/6 vs. 0/5 - $p < 0.05$). On the other hand, the incidence of portal hypertension gastropathy was significantly more frequent in the sclerotherapy group (16% vs. 6% - $p < 0.05$), as was the risk of bleeding at this site ($p < 0.05$). Although this was a controlled study, the endoscopic classification of varices was not described, patients with grade IV LV were excluded, and 88% of patients had compensated cirrhosis (Child A). Therefore, patients with a higher risk of bleeding were excluded. The authors justified the exclusion of patients with Grade IV varicose veins due to the expected worse prognosis, greater chance of bleeding after the procedure and the allegation of ethical reasons, since they could be allocated to the control group, without any treatment²⁷.

The remaining studies analyzed are retrospective, with several methodological limitations, and are presented in chronological order of publication in Table 2³⁰⁻⁴⁴. The most relevant studies and those with the largest number of patients are detailed below.

In 2013 Duche *et al.*³⁶ published a retrospective study of primary and secondary prophylaxis in 66 children with biliary atresia between 2001 and 2011. Data were collected from children with portal hypertension and grade 3 or grade 2 LV with red spots and/or gastric varices who received prophylactic endoscopic treatment. Thirty-six children (mean age, 15 months) underwent primary endoscopic prophylaxis. EGD was performed under general anesthesia and continuous infusion of octreotide at 2 mcg/kg/h, started 1 hour before the procedure and gradually reduced to 1 mcg/kg/h after 2–3 days, according to the service protocol. There were no reports of side effects secondary to octreotide. Prophylaxis was performed with sclerotherapy or LEVE, depending on age and weight. Varicose vein eradication occurred in 27/36 children (75%), with a mean number of 4.2 sessions required to achieve eradication. There were no episodes of UGIB after eradication in this group during the mean follow-up of 28 months. Only minor complications were detected after the procedure: 2 children (6%) presented early bleeding after the procedure due to incomplete variceal control, and one had a transient episode of fever after sclerotherapy. Varicose vein recurrence occurred in 37% of the children, with an interval ranging from 1 to 89 months. There was no emergence of gastric varices during follow-up. The probability of survival at 3 years was 97% in the group that received primary prophylaxis³⁶.

In 2017 Shower *et al.*³⁷ published a new study that followed 1,300 children with portal hypertension, both cirrhotic and non-cirrhotic, from 1989 to 2014. The aim was to describe the endoscopic predictors of UGIB, the complications of bleeding episodes, and the experience with primary prophylaxis in 170 children who had never bled and had high-risk varices: 120 cirrhotic and 50 with EHPVO or congenital hepatic fibrosis. The approach depended on the cause of portal hypertension and could be surgical, radiological, or endoscopic (sclerotherapy or LEVE). No beta-blockers were used. Primary endoscopic prophylaxis with sclerotherapy or LEVE was performed in 23 of 50 non-cirrhotic patients, with eradication achieved in 22 (95.7%) of them; recurrence occurred in 6 patients (26%), with one episode of UGIB after recurrence. The mean follow-up of these patients was 4.1 years (0.75–15 years), with no deaths during the follow-up period. Among cirrhotic patients, endoscopic prophylaxis was administered to 110/120 patients, with eradication achieved in 76 of them (69%). Recurrence of high-risk varices occurred in 40% of children who underwent eradication. The mean follow-up of these patients was 4.5 years (0.1–20 years). The probability of bleeding-free survival at 10 years after primary endoscopic prophylaxis in children with high-risk varices was 96% for children without cirrhosis and 72% for children with cirrhosis. The probability of overall survival at 10 years after primary prophylaxis was 100% in children without cirrhosis and 93% in those with cirrhosis. With the publication of these various works, the French group consolidates itself as one of the main research services and advocates of primary prophylaxis³⁷.

The study by Quintero *et al.*¹¹ has been previously presented. Here, we present the prospective arm (2009–2013) that evaluated ligation as primary prophylaxis with a minimum follow-up of 1 year. In the LEVE group, 31 of 32 patients (96.8%) did not present UGIB. Only one patient had a minor bleeding episode six days after the ligation procedure, due to the fall of one of the elastic bands. Twenty-four patients (75%) achieved variceal eradication, with a median of 2 procedures (range, 1–4) before eradication and a median time to eradication of 3.4 months (range, 1.10–13.33). No adverse effects of ligation were observed, except for retrosternal pain in two patients, which improved with a single dose of conventional analgesia. Two patients had recurrence of EV without UGIB 2 and 6 months after eradication. Statistically significant differences were observed in the bleeding rate between the propranolol and ligation groups (6/32 [21.9%] vs. 1/32 [3.2%], $p < 0.02$), but no significant differences were observed in survival at 1 and 3 years of follow-up between the two groups. The probability of UGIB was higher in the propranolol group. However, the previously highlighted methodological limitations of the retrospective propranolol control group should be borne in mind¹¹.

A retrospective North American study published in 2022⁴³ (with data from 1994 to 2019) evaluated 87 children receiving primary endoscopic prophylaxis with LEVE or sclerotherapy compared with 52 children receiving secondary prophylaxis. The median number of UGIE in the primary prophylaxis group was lower than in the secondary prophylaxis group (3 vs. 6, $p = 0.005$). Primary prophylaxis was associated with a lower number of UGIE episodes compared to secondary prophylaxis (24% vs. 51%, $p = 0.02$) and significantly fewer pediatric intensive care unit admissions (1% vs. 7%, $p < 0.001$). Few patients achieved complete variceal eradication, only 7% in the primary prophylaxis group, partly due to the number of patients who were still in the early eradication phase at the end of the study. There were no deaths related to UGIB or complications of UGIB. There was better overall survival ($p = 0.023$) and survival with native or shunt-free liver ($p < 0.001$) in the primary prophylaxis group, even when patients with EHPVO were excluded, contrary to the results of Chen *et al.*⁴².

In 2022 it was published by the French group Ackermann *et al.* (2022), a retrospective study of 145 children with portal hypertension who underwent primary prophylaxis between 2006 and 2019⁴⁴. The median age of the patients followed was 3.7 years (range, 4 months to 17 years), and 116 (80%) of these patients were cirrhotic, 95 (65.5%) with biliary atresia. Each session was performed under general anesthesia, with continuous infusion of intravenous octreotide according to a protocol previously evaluated by the group³⁷. Primary endoscopic prophylaxis was performed with LEVE in 114 children (median age, 5 years, range, 6 months to 17 years) and sclerotherapy in 31 children (median age, 9 months, range, 3.5 months to 7 years); the latter mainly in children weighing less than 8 kg. The high-risk score was used to assess endoscopic

Table 2. Studies on primary endoscopic prophylaxis of variceal gastrointestinal bleeding in children and adolescents.

Studies	Drawing and Technique used	N	Eradication	Relapse	HDA	Follow-up Time	Observations
Howard <i>et al.</i> (1998)³⁰ England	Case series 1 st and 2 nd prophylaxis ET	17	11 patients (64.7%) after an average number of 3.8 sessions	No data	No data	Average 2.5 years	No data on HDA, relapse and adverse effects of 1 st and 2 nd prophylaxis separately
Maksoud <i>et al.</i> (1991)³¹ Brazil	Retrospective ET	26	92.3% after an average of 4.7 sessions	No data	42.3% 8 deaths (2 due to HDA)	1.9 years	Paquet grade 3 or 4 LV
Sasaki <i>et al.</i> (1998)³² Japan	Retrospective LIGHT	11 children with AB: 9 prophylactic	8 of 11 (72.7%)	No data	1 episode of HDA due to elastic band slippage with massive hemorrhage	Not informed	Only children with AB, average age 7.8 years
Goncalves <i>et al.</i> (2000)²⁷ Brazil	Prospective, randomized ET X control	100 children with VE < grade 4 50 ET 50 control 37/100 had biliary atresia 88/100 Child A - only 1 Child C 9/100 OEHVP	47 out of 50 children (94%)	No data	ET reduced the risk of UGIB (24% X 48% - p<0.05), but did not improve mortality (18% X 16% - p> 0.05).	Median 36 months (ranging from 18 months to 8 years)	Patients with higher risk of bleeding were excluded (VE < grade 4 and only 1 Child C) ET did not increase the incidence of VG (p>0.05), but when present, there was a higher risk of bleeding (p<0.05). HP gastropathy was more frequent in the ET group (16% X 6% - p<0.05), as was the risk of bleeding at this site (p<0.05).
Celinska Cedro <i>et al.</i> (2003)³³ Poland	Prospective LIGHT	37 children aged 4 to 7 (22 cirrhosis and 15 OEHVP)	90.3% after 2 LEVE sessions at 3-month intervals	Recurrence of varices without bleeding in 3 (8.1%) children	No episodes	16 months after stopping prophylactic treatment	4 patients underwent liver transplantation before eradicating varicose veins 16 children in the study were previously treated with propranolol but still met the inclusion criteria Short follow-up time
Duché <i>et al.</i> (2008)³⁴ France	Prospective ET	13 AVB infants	8 (61.5%) eradicated varicose veins Average of 4.2 sessions	No data	0/8 that eradicated 2/5 that did not eradicate (1 death)	No data	Small number of patients, but homogeneous population (infants with BA and mostly with end-stage liver disease)

Mckiernan et al. (2011) ²⁸ United Kingdom	Prospective, randomized, multicenter LIGHT	12 prophylaxis 1 st X 10 control	No data	No data	1 of 12 (8.3%) in the prophylaxis group 3 of 10 (30%) in the large-caliber varicose vein group without prophylaxis	2 years	Pilot study 1 of 12 (8.3%) children in the prophylaxis group died from causes unrelated to prophylaxis
Lampela et al. (2012) ³⁵ Finland	Retrospective ET	16 AB primary prophylaxis	No distinction between primary and secondary prophylaxis	No distinction between primary and secondary prophylaxis	4 of the 16 (25%) patients on primary prophylaxis had UGIB during follow-up, all belonging to the group with failed portoenterostomy.	Average of 1.7 years	
Duché et al. (2013) ³⁶ France	Retrospective, single-centered ET or LEVE	36 with AB	27/36 children (75%)	37%.	No HDA after eradication	Average of 28 months	AB only, not randomized Average number of 4.2 sessions to eradicate
Duché et al. (2017) ³⁷ France	Retrospective, ET or LEVE	Cirrhotics 110 Non-cirrhotic 23	Cirrhotics: 76/110 (69%) Non-cirrhotic: 22/23 (95.7%)	Cirrhotics: 40% Non-cirrhotic: 26%	Cirrhotics: 20/110 HDA - 18.2% (17 at the beginning of treatment and 3 after relapse) 5 deaths from HDA Non-cirrhotic: 1 (4.3%) HDA	Cirrhotics 4.5 years (0.1-20 years) Non-cirrhotic: 4.1 (0.75-15) years	AVB Majority 34 did not eradicate - 3 deaths and 29 underwent liver transplantation before eradication was completed, 1 TIPS
Galand et al. (2017) ³⁸ France	Retrospective LEVE	30	17% eradication 77% reduced number or degree	No data	17%	4.9 years	There was no significant difference in HDA-free survival between 1st and 2nd prophylaxis 70% used beta-blockers in combination
Prasad et al. (2019) ³⁹ India	Retrospective LIGHT	11 primary prophylaxis in non-cirrhotic portal fibrosis	100%	36%	Death in 3 children from HDA before eradication	48 months	
Quintero et al. (2020) ⁴¹ Spain	Retrospective Prospective LEVE X Propranolol	64 - 32 in each group	75% Median of 2 sessions	6.5%	UGIB in the propranolol group 7/32 (21.9%) Risk of UGIB for propranolol X MILD 2.6 (95% CI, 1.53-3.67)	Not informed Minimum of 1 year	There was no significant difference observed in survival at 1 and 3 years of follow-up between the two groups
Oliveira et al. (2020) ⁴⁰ Brazil	Prospective cohort LIGHT	14 primary prophylaxis with OEHVP	85.7%, average number of 3.5 sessions to eradicate.	41.7%	14.7%	5.7 years	Cohort followed for 12 years.

Lee et al. (2021)⁴¹ Malaysia	Retrospective LIGHT and ET	16 (1 with VE grade I and 4 grade II who lived far from the center) 6 OEHP and 5 AB	No data	1/16 6.2%	Probability of bleeding compared to 2nd prophylaxis (1/16 X 14/38, p=0.022)	8.9 + -4.7 years	Lower number of EDA repetitions in the 1st prophylaxis than in the 2nd (p=0.021) no difference in overall survival or with native liver between 1st and 2nd prophylaxis (p=0.33 and 0.39 respectively)
Chen et al. (2022)⁴² Taiwan	Retrospective LIGHT	38	No data	No data	14.4% in primary prophylaxis and 32.4% in secondary prophylaxis p=0.38	Median 12.5 years	First prophylaxis without impact on overall or transplant-free survival (p=0.39 and 0.49) compared to second prophylaxis
Slowik et al. (2022)⁴³ United States	Retrospective ET or LEVE	87	7%	No data	24%	Median 2.13 years	Improvement in overall survival and survival with native liver in primary prophylaxis compared to 2 nd
Ackerman et al. (2022)⁴⁴ France	Retrospective ET or LEVE	145	93% after 6 months	45%	17%	Median 3.7 years	All received octreotide during the procedure Grade 3 LV had a worse probability of eradication and varicose veins along the cardia required longer time to eradicate

AB: biliary atresia; EDA: Upper gastrointestinal endoscopy; ET: sclerotherapy; LEVE: esophageal variceal band ligation; UGIB: upper gastrointestinal bleeding; HP: portal hypertension; EHVP: extrahepatic portal vein obstruction; Transjugular TIPS intrahepatic portosystemic shunt; LV esophageal varices.

severity Varices (HRV) was calculated as follows: one point for grade 1 esophageal varices, two points for grade 2, three points for grade 3, and one point for the presence of red spots or gastric varices along the cardia. Variceal eradication was achieved in 135 (93%) of the children, with a mean time of 6 months, requiring 1-8 sessions; the number of sessions required for eradication was lower in the ligation group compared to the sclerotherapy group, although the protocols and intervals between sessions differed between the methods. Variceal recurrence occurred in 45% of the children; the first recurrence was recorded between two months and five years after eradication; there was no significant difference in the risk of the first recurrence in cirrhotic and non-cirrhotic patients (p=0.97). UGI occurred in 26/145 patients (17%) during the follow-up period: 15/26 during the initial endoscopic treatment period; 7/26 after variceal recurrence; and 4/16 from other sites (ectopic varices, gastropathy, or duodenal ulcer). Regardless of the cause of portal hypertension, grade

3 esophageal varices had a worse probability of eradication (p=0.02). Adverse effects were rare: fever (2 patients), mucosal ulcer (6 patients), esophageal stricture (1 patient), and esophageal perforation with pleural effusion (1 patient). The study mortality rate was low, with 3.4% death from other causes. The 10-year overall survival probability after the first treatment session was 95%, and that of UGI-free survival was 75%. In multivariate analysis, a lower HRV score was associated with better UGI-free survival. In children with cirrhosis, prothrombin activity was associated with a higher risk of severe bleeding (resulting in death or need for urgent liver transplantation): a mean activity of 65% in patients with severe events vs. 82% in patients without UGIB (p=0.002), maintained in the multivariate analysis. In the discussion, the authors argue that there is no doubt that, in children with cirrhosis, UGIB has many serious consequences, with increased morbidity and mortality within 6 weeks of bleeding. Therefore, primary UGIB prophylaxis in at- risk children should be considered⁴⁴.

In children with EHPVO, a surgical *shunt such as the Meso-rex* should be attempted. Because endoscopic severity of varices has been associated with worse eradication outcomes, the authors suggest an early approach by detecting noninvasive predictors of portal hypertension in at-risk children, even in the first months of life, so that screening UGIB can be performed before endoscopic signs are too advanced. It is important to emphasize that the risk of varicose vein recurrence persists after endoscopic treatment, unless definitive treatment such as liver transplantation or surgical shunt is performed. Therefore, prolonged endoscopic surveillance is necessary to detect and treat recurrences. For children with cirrhosis, with a severe endoscopic pattern and low prothrombin activity, the authors suggest expediting referral for liver transplantation. With these caveats, the group advocates primary prophylaxis⁴⁴ in contrast to the North American group¹⁵. Several factors should be considered in this discussion, such as the risk of UGIB in patients with cirrhosis and EHPVO, morbidity and mortality of episodes, geographic distance of patients from referral centers, and, finally, the efficacy of the approaches.

Overall, primary endoscopic prophylaxis in the studies evaluated presented few complications and good results in varicose vein eradication. However, the high risk of varicose vein recurrence persists. Contrary to previous belief, these studies did not show a high risk of bleeding from gastric and ectopic varices.

CONCLUSIONS

There is no consensus on primary pharmacological or endoscopic prophylaxis of variceal UGIB in the pediatric population. Pharmacological prophylaxis with propranolol has shown many challenges: side effects, difficulty achieving beta-blockade, and, in some studies, low effectiveness in reducing the risk of UGIB. Few studies have been published, most of them retrospective case series, with only one randomized clinical trial. It is unclear whether the hemodynamic pathophysiology in children with cirrhosis and portal hypertension is the same as in adults. The reduction in cardiac output caused by beta-blockers can potentially be harmful to children, preventing compensatory tachycardia during variceal UGIB. Furthermore, side effects such as bronchospasm, hypoglycemia, and hypotension are common, leading to discontinuation of the medication. Therefore, the available pediatric data are inconclusive and still too limited to support the routine use of beta-blockers as primary prophylaxis for variceal UGIB. Most services have abandoned the practice, which is still the method of choice in the adult population, as it is associated with better outcomes and prevention not only of UGIB but also of other complications of portal hypertension.

Primary endoscopic prophylaxis through sclerotherapy or LEVE is more commonly used, especially in Europe and Brazil. LEVE has been the primary prophylaxis method of

choice for most centers performing the procedure. It is important to note that, in most of the studies analyzed, there were high rates of varicose vein recurrence, since the cause, portal hypertension, is not addressed. Eradication of varicose veins requires multiple endoscopic procedures, usually under general anesthesia, which carry their own risks and costs. Furthermore, although uncommon, complications such as esophageal ulceration, stricture, or perforation can occur after endoscopic procedures.

North American study groups generally consider the low mortality rate in the pediatric population, and many do not perform primary prophylaxis for this reason. Furthermore, a study already cited in this review considered the incidence of UGIB in patients with biliary atresia to be low. However, we must consider the differences in the scenarios evaluated: in developed countries with greater access to the healthcare system, portoenterostomy surgeries are performed early, increasing the chance of success, as are liver transplants, modifying the prognosis for these patients. Although the mortality rate from UGIB episodes in the pediatric population cannot be considered high, morbidity is considerable, involving length of hospital stay, infection, ascites, encephalopathy, and the need for invasive ventilation¹²⁻¹⁴.

European countries, on the other hand, tend to perform primary endoscopic prophylaxis. The group with the largest case series is the French group from the Bicêtre Hospital in Paris, which demonstrated good safety, with rare adverse effects and high varicose vein eradication rates^{37,44}. Brazilian groups, in general, also tend to perform primary endoscopic prophylaxis^{27,31,40}. It is important to always weigh the risk-benefit of the procedure, which is not without complications, but can considerably improve the quality of life of these patients.

While important, conducting randomized controlled clinical trials in the pediatric population is not straightforward. A large sample size is required, considering losses to follow-up due to liver transplantation, deaths, and surgical *shunts*, which would only be feasible in a multicenter study. Future research should address issues such as natural history, risk of variceal bleeding, efficacy of primary prophylaxis, and improved survival and quality of life in these patients.

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