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Endoscopic Primary Prophylaxis to Prevent Bleeding in Children with Esophageal Varices: A Systematic Review and Meta-Analysis

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Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Purpose: This systematic review and meta-analysis aimed to compare endoscopy as primary versus secondary prophylaxis to prevent future bleeding in children with esophageal varices.
Methods: A systematic literature search using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses method was conducted using the Scopus, PubMed, and Cochrane databases for relevant studies on the outcome of rebleeding events after endoscopy in primary prophylaxis compared to that in secondary prophylaxis. The following keywords were used: esophageal varices, children, endoscopy, primary prophylaxis and bleeding. The quality of eligible articles was assessed using the Newcastle–Ottawa Scale and statistically analyzed using RevMan 5.4 software.
Results: A total of 174 children were included from four eligible articles. All four studies were considered of high-quality based on the Newcastle-Ottawa Quality Assessment Scale. Patients who received primary prophylaxis had 79% lower odds of bleeding than those who received secondary prophylaxis (odds ratio, 0.21; 95% confidence interval [CI], 0.07–0.66; I^2=0%, p=0.008). Patients in the primary prophylaxis group underwent fewer endoscopic procedures to eradicate varices than those in the secondary prophylaxis group, with a mean difference of 1.73 (95% CI, 0.91–2.56; I^2=62%, p<0.0001).
Conclusion: Children with high-risk varices who underwent primary prophylaxis were less likely to experience future bleeding episodes and required fewer endoscopic procedures to eradicate the varices than children who underwent secondary prophylaxis.

Keywords: Hemorrhage; Child; Endoscopy; Primary prevention

INTRODUCTION

Esophageal varices (EV) are a major complication in patients with portal hypertension (PH) due to chronic liver disease [1]. In children, biliary atresia (BA) and extrahepatic portal vein obstruction (EHPVO) are the most common causes of PH [2]. Approximately 200,000 children experience variceal bleeding annually due to PH, particularly upper gastrointestinal bleeding. In the first two years following portoenterostomy, nearly 20% of patients with BA who did not require liver transplantation experienced variceal hemorrhage [3]. The recommended methods for managing children with variceal hemorrhage and PH are still

highly debatable [4]. Due to a lack of evidence-based recommendations, there is no standard procedure for the screening and prophylactic management of EV in pediatric patients [1,3].

Some studies have reported a low mortality risk after a child's first variceal hemorrhage. This low mortality rate is mostly due to the availability of medical treatment, caregivers' response to bleeding symptoms, and proactive parents who seek immediate emergency medical treatment for bleeding [4]. Thus, the choice of primary prophylaxis to prevent bleeding in children needs to be meticulously investigated. Beta-blockers, endoscopic sclerotherapy, and endoscopic variceal ligation are techniques used as primary prophylaxis to prevent bleeding in children [3,4]. The use of beta-blockers in children is still not advised because of their possible toxicity due to the lack of standardized measurements of appropriate doses related to the reduction of heart rate and the potential of hypotension in the case of a significant amount of blood loss [3].

Endoscopy is the gold standard for diagnosing EV; however, it has not been widely used due to its invasiveness and the lack of data on the efficacy and safety of follow-up therapy to stop bleeding in children with varices [3,4]. Furthermore, according to a study by Lee et al. [2], children with EV who underwent endoscopic sclerotherapy or band ligation had lesser future spontaneous rebleeding and required fewer subsequent endoscopic procedures than those who received secondary prophylaxis. Therefore, this study aimed to evaluate endoscopic primary prophylaxis to prevent future bleeding episodes in comparison to secondary prophylaxis.

MATERIALS AND METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement was used to conduct this systematic review and meta-analysis [5].

Data sources and literature search

We performed a systematic literature search of three international databases (PubMed, Scopus, and Cochrane) using the following keywords based on population, intervention, control, and outcome: EV, children, endoscopic, primary prophylaxis, and bleeding on December 21, 2022. **Supplementary Table 1** lists the specific search queries for the various databases. Articles from the search results were screened for duplicate publications and reviewed for relevant articles based on the inclusion and exclusion criteria.

Study selection and data extraction

We included randomized controlled trials, cohort studies (retrospective or prospective), and case-control studies that compared endoscopic primary prophylaxis with secondary prophylaxis to prevent bleeding outcomes. We excluded duplicate studies, conference abstracts, editorials, brief research letters, and studies written in languages other than English. The eligibility of articles was determined by two reviewers (LO and EM). Any differences were resolved through discussions with another author (FSA). A standard data extraction Excel sheet was produced using Microsoft Excel and two reviewers independently extracted the data (LO and EM). The extracted information included the first author, study year, country of origin, study design, study population, age at onset of prophylaxis, total number of subjects in each group, number of bleeding incidents following prophylactic procedures, and total number of endoscopies needed.

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Quality assessment

After initial extraction, all eligible studies were evaluated using the modified Newcastle-Ottawa Scale (NOS). For each study, a separate quality assessment was conducted by two authors. Low-quality studies were defined as those with NOS scores <7.

Definition of primary and secondary prophylaxis

Primary prophylaxis was defined as either endoscopic band ligation or sclerotherapy performed before the first bleeding episode. In contrast, secondary prophylaxis was defined when these procedures were conducted after the first bleeding episode to prevent future bleeding.

Outcomes

Rebleeding incidents after the first endoscopic prophylaxis, both primary and secondary, were the outcomes of interest. The secondary outcome was the total number of endoscopies required during the study period.

Statistical analysis

The effects of endoscopy on primary and secondary prophylaxis were examined using the pooled effect sizes. Sensitivity analysis was used to investigate heterogeneity of the results. The impact of high-quality evidence was investigated using a subgroup analysis that evaluated only high-quality studies. Meta-analyses were performed only when two or more studies were available for each outcome. Odds ratios (OR) were calculated for dichotomous variables. We calculated the OR using a random-effects model with the Mantel-Haenszel method, assuming that studies from various populations worldwide would be heterogeneous. The mean difference was calculated for the quantitative data.

The I^2 statistic was used to assess the statistical heterogeneity between studies. Substantial heterogeneity among the trials was defined as an I^2 statistic >50%. Funnel plot visualization and the test for funnel plot asymmetry (also known as Egger's test) were utilized [6].

The funnel plot asymmetry test does not have statistical power to identify bias in the case of a limited number of studies. Hence, we did not examine publication bias if the number of studies for any outcome was <10 [7]. Meta-analysis was considered statistically significant if the *p*-value was <0.05. Data were analyzed using the RevMan 5.4 software (The Cochrane Collaboration).

RESULTS

Literature search

A literature search was performed using three international research databases, resulting in 44 studies. After screening titles, 16 duplicate studies were excluded. Another 16 were excluded because they were not relevant to the research questions. Eight articles were further disqualified because there were no desired outcomes or use of beta-blockers for comparison. Finally, four studies were included in this systematic review and meta-analysis (**Fig. 1**).

Population and study characteristics

The populations were similar across all studies and consisted of children with gastroesophageal varices and PH. Of the 174 children included in these studies, 57 (32.7%) underwent primary prophylaxis, while the other 117 (67.3%) underwent secondary prophylaxis. Primary prophylaxis was defined as endoscopic band ligation or sclerotherapy

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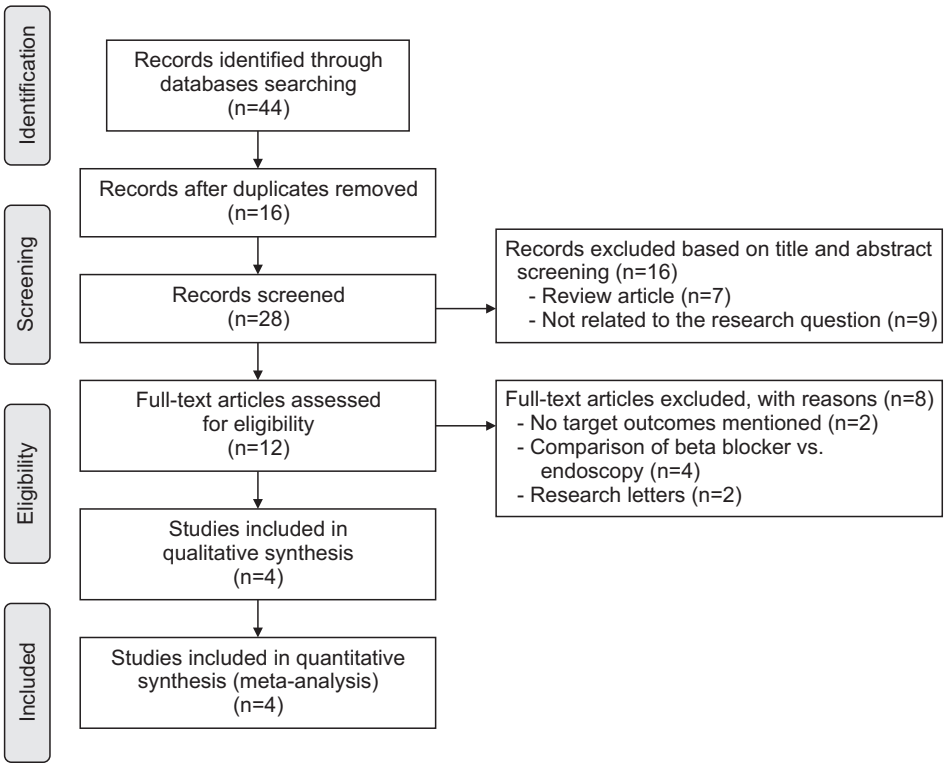

Fig. 1. PRISMA diagram.
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

performed before the first bleeding episode. In contrast, secondary prophylaxis was defined as when the procedures were conducted after the first bleeding episode to prevent future bleeding. The indications for primary prophylaxis were similar in all studies. Primary prophylaxis by either endoscopic band ligation or sclerotherapy was performed when there were signs of major bleeding risks (grade III esophageal varices or varices extending to the gastric cavity or the presence of cherry-red spots (red wales) on the varices). Additionally, Lee et al. [2] conducted primary prophylaxis for patients living in areas where there was a lack of access to emergency endoscopy in the event of upper gastrointestinal bleeding.

The diseases underlying PH varied among studies. Angelico et al. [8] conducted their study on children with PH due to BA who were waiting to undergo transplantation. In contrast, de Oliveira et al. [9] performed their study on children with EHPVO, Prasad et al. [10] on children with noncirrhotic portal fibrosis, and Lee et al. [2] on children with varying underlying diseases (BA, nonbiliary atresia cirrhosis, and EHPVO). The characteristics of the study population are presented in **Table 1**.

All four studies were single-centered, three were retrospective, and one was prospective. All studies were considered of high quality based on the Newcastle-Ottawa Quality Assessment Scale (**Supplementary Table 2**).

Outcomes

1. Bleeding

Three studies reported the rate of bleeding during the follow-up period and during or after the prophylaxis procedure. The pooled incidence of bleeding in the primary and secondary

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Table 1. List of studies and population characteristics

Study, year	Country	Design	Population	Mean age (SD) at onset of prophylaxis		Total subjects		Bleeding incidence		Mean (SD) number of endoscopies	
				Primary prophylaxis	Secondary prophylaxis	Primary prophylaxis	Secondary prophylaxis	Primary prophylaxis	Secondary prophylaxis	Primary prophylaxis	Secondary prophylaxis
Angelico et al. [8], 2019	Italy	Retrospective	Children with portal hypertension, biliary atresia, and liver transplant candidates	11.2 (9.2) mo	10.7 (8.2) mo	16	16	1	4	1 (1.3)	2 (1.0)
Oliveira et al. [9], 2020	Brazil	Prospective	Children with portal hypertension and extrahepatic portal vein obstruction	1.6 (0.8) y	2.1 (0.7) y	14	41	2	14	3.2 (1.5)	4.4 (2.0)
Lee et al. [2], 2021	Malaysia	Retrospective	Children with portal hypertension	4.5 (4.5) y	5.5 (4.7) y	16	38	1	14	0.9 (1.0)	3.1 (2.5)
Prasad et al. [10], 2020	India	Prospective	Children with portal hypertension and non-cirrhotic portal fibrosis	13.5 (0.8) y	15 (2.5) y	11	22	Not available	Not available	4 (1.7)	7 (2.5)

SD: standard deviation.

prophylaxis groups was 8.7% (4/46) and 33.7% (32/95), respectively. Patients who received primary prophylaxis had 79% lower odds of bleeding than those who received secondary prophylaxis (OR, 0.21; 95% confidence interval [CI], 0.07-0.66; I^2=0%, p=0.008) (**Fig. 2**).

2. Number of endoscopies

Four studies reported the number of endoscopies required for the first eradication of gastroesophageal varices. Patients in the primary prophylaxis group had to undergo fewer endoscopic procedures to eradicate varices than those in the secondary prophylaxis group, with a mean difference of 1.73 (95% CI, 0.91-2.56; I^2=62%, p<0.0001) (**Fig. 3**).

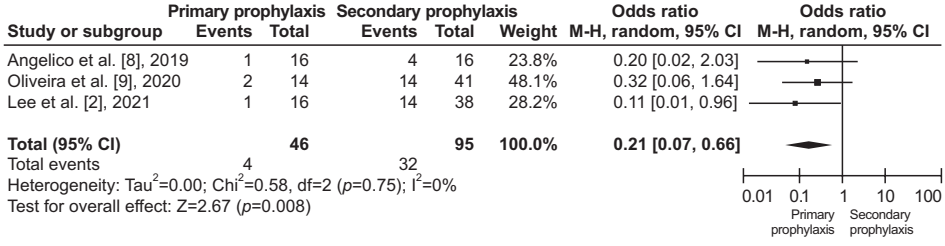

Fig. 2. Forest plots for bleeding incidence outcomes.
CI: confidence interval.

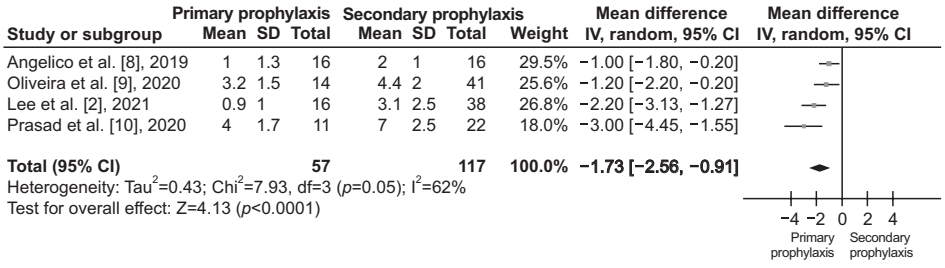

Fig. 3. Forest plots for number of endoscopy outcomes.
SD: standard deviation, CI: confidence interval.

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3. Assessment of evidence by Grading of Recommendations Assessment, Development and Evaluation (GRADE)

The GRADE methodology was used to evaluate the certainty of the evidence for each outcome. Three studies included in this meta-analysis were retrospective, and only one was prospective. Nevertheless, all studies were ranked as high quality based on the Newcastle-Ottawa Scale. Bleeding outcomes and the number of endoscopies were uniformly defined across all studies. The indications for primary prophylaxis and the study populations were also similar between the studies. However, the underlying diseases differed across studies.

The risk of bias was low and insufficient to downgrade the certainty of evidence as all studies applied the appropriate eligibility criteria with a uniform measurement of exposure and outcome. Moreover, the follow-up duration was long enough to observe the outcomes of all studies. Based on the heterogeneity analysis, all four studies were considered homogeneous in terms of population, intervention, and outcomes. Indirectness, imprecision, and publication bias were also not serious enough to lower the certainty of the evidence in this meta-analysis. Therefore, after evaluation by GRADE analysis, the certainty of outcome of bleeding and the number of endoscopies were rated “low.”

DISCUSSION

Primary prophylaxis by either endoscopic ligation or nonselective beta-blockers has been the standard protocol for adults, considering the numerous clinical trials in adults that have proven the advantages of these treatments in preventing the first episode of variceal bleeding. However, the use of primary prophylaxis in children is still controversial due to a lack of data regarding the safety and efficacy of that treatment, as most data are extrapolated from adult studies [3]. There are limited data on whether endoscopic procedures should be performed before the first episode of variceal bleeding as primary prophylaxis or after the first episode of variceal bleeding as secondary prophylaxis.

This meta-analysis proved that endoscopic primary prophylaxis is superior to secondary prophylaxis in reducing the incidence of future variceal bleeding. This may be explained by the fact that endoscopic primary prophylaxis was administered to children with signs of a high risk of bleeding. Several other studies have reported similar results. One study by Duche et al. [11] justified the use of primary prophylaxis, as it had proven to provide children with bleeding-free survival rates as high as 96% for non-cirrhotic and 72% for cirrhotic patients during ten years of follow-up. Moreover, a randomized prospective trial demonstrated that primary prophylactic sclerotherapy effectively eradicated 94% of EV, with 76% of the patients free of upper gastrointestinal bleeding by the end of the study [12].

The decision to administer primary prophylaxis should be considered particularly for patients with high-risk varices. Variceal bleeding is a serious clinical occurrence that can have life-threatening effects, requiring blood transfusion and admission to the intensive care unit. One study on children with BA reported that 43.8% of spontaneous gastrointestinal varices bleeding were life-threatening and required admission to the intensive care unit [8]. Furthermore, among North American children with liver impairment of various causes, a death rate of 19% has been documented within 35 days of variceal hemorrhage episodes [13]. Even in cases of non-life-threatening hemorrhage, upper gastrointestinal bleeding can impose psychological anguish on the patient and family [14].

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This meta-analysis also demonstrated that children receiving primary endoscopic prophylaxis required fewer repeated endoscopic procedures than those receiving secondary prophylaxis. This provides benefits for both patients and the healthcare system. Patients do not have to experience gastrointestinal bleeding, and in the long term, less psychological trauma with fewer endoscopic procedures [2]. For the healthcare system, fewer endoscopic procedures may ultimately lead to a cost reduction [2].

The main limitation of this study is that most of the included studies had a retrospective design. Moreover, the results of these studies may also be affected by selection bias when selecting the population that underwent primary prophylaxis. In all of these studies, primary prophylaxis was reserved for patients with a high risk of bleeding. However, the indications for endoscopic screening procedures to detect high-risk varices varied across all studies, as there were no standardized protocols for routine screening. Therefore, a selection bias may have occurred when selecting patients who underwent endoscopic screening to detect high-risk varices.

This is the first systematic review and meta-analysis to evaluate the benefits of endoscopic primary prophylaxis in children with varices and PH caused by various liver diseases. Hence, this review may serve as a foundation for further advocating the use of endoscopic primary prophylaxis to prevent variceal bleeding in the first place and reduce the cost burden with fewer long-term endoscopic procedures.

In conclusion, this meta-analysis demonstrated that children with high-risk varices who underwent primary prophylaxis were less likely to experience future bleeding episodes and required fewer endoscopic procedures to eradicate these varices than children who underwent secondary prophylaxis. However, further investigations are needed to determine the criteria for which patients should undergo endoscopic screening to detect high-risk varices. The certainty of evidence in this review was graded as low because of the retrospective nature of most studies and the small number of subjects in each study.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Literature search strategy

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Supplementary Table 2

Newcastle-ottawa scale appraisal for each study

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