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Primary Prophylaxis of Variceal Hemorrhage in Children With Portal Hypertension: A Framework for Future Research

Simon C. Ling[*], **Thomas Walters**[*], **Patrick J. McKiernan**[†], **Kathleen B. Schwarz**[‡], **Guadalupe Garcia-Tsao**[§], and **Benjamin L. Shneider**[||]

[*]Division of Gastroenterology, Hepatology & Nutrition, The Hospital for Sick Children, Toronto, Ontario, Canada

[†]The Liver Unit, Birmingham Children's Hospital, Birmingham, UK

[‡]Department of Pediatric Gastroenterology, Johns Hopkins University Hospital, Baltimore, MD

[§]Digestive Diseases Section, Yale University School of Medicine, New Haven, CT

[||]Department of Pediatric Gastroenterology, Children's Hospital of Pittsburgh, Pittsburgh, PA

Abstract

Nonselective β-blocker therapy and endoscopic variceal ligation reduce the incidence of variceal hemorrhage in cirrhotic adults, but their use in children is controversial. There are no evidence-based recommendations for the prophylactic management of children at risk of variceal hemorrhage due to the lack of appropriate randomized controlled trials. In a recent gathering of experts at the American Association for the Study of Liver Diseases annual meeting, significant challenges were identified in attempting to design and implement a clinical trial of primary prophylaxis in children using either of these therapies. These challenges render such a trial unfeasible, primarily due to the large sample size required, inadequate knowledge of appropriate dosing of β-blockers, and difficulty in recruiting to a trial of endoscopic variceal ligation. Pediatric research should focus on addressing questions of natural history and diagnosis of varices, prediction of variceal bleeding, optimal approaches to β-blocker and ligation therapy, and alternative study designs to explore therapeutic efficacy in children.

Keywords

endoscopic variceal ligation; esophageal varices; nonselective β-blockers; portal hypertension; primary prophylaxis; variceal bleeding

Primary prophylaxis of variceal hemorrhage in adults is the established standard of care, following numerous controlled clinical trials demonstrating the efficacy of nonselective β-blocker therapy and endoscopic variceal ligation (EVL) in decreasing the incidence of variceal hemorrhage (1). Although the majority of North American pediatric hepatologists report a willingness to offer these therapies to selected pediatric patients with portal hypertension (2), the widespread use of primary prophylaxis in children is controversial due

Address correspondence and reprint requests to Simon C. Ling, MBChB, Dept of Gastroenterology, Hepatology, & Nutrition, The Hospital for Sick Children, 555 University Ave, Toronto, ON, Canada M5G 1X8 (simon.ling@sickkids.ca).

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to the lack of pediatric data and the wariness among pediatricians of extrapolating results of adult studies to children (3).

In November 2009, a focused study group convened at the annual meeting of the American Association for the Study of Liver Diseases to address the feasibility of a randomized controlled trial of primary prophylaxis of variceal hemorrhage in children. The group's discussions are presented here, with the aim of building upon recent reviews of the published research into variceal hemorrhage and its prevention in children (4–6). We conclude by presenting a framework for further investigations to define more clearly the need for and appropriate design of a future clinical trial.

EVOLUTION OF PRIMARY PROPHYLAXIS FOR ADULTS WITH CIRRHOSIS

The development of therapies to prevent variceal hemorrhage in adults was initially prompted by the high incidence of variceal bleeding and the associated high mortality rate, and occurred in parallel with the advancement of understanding of the pathophysiological mechanisms of portal hypertension. Early approaches concentrated on portosystemic shunt surgery to reduce portal pressure. Studies showed that this procedure effectively reduced bleeding rates but with an unacceptably increased risk of hepatic encephalopathy and death (7). Surgical shunts are therefore no longer recommended for primary prophylaxis.

Medical approaches to prophylactic therapy arose from an understanding that vascular resistance in the portal system is elevated by the distorted hepatic architecture of cirrhosis, intrahepatic small-vessel thromboses, and increased intrahepatic vascular tone arising from the actions of vasoactive substances on myofibroblasts, perisinusoidal activated stellate cells, and vascular smooth muscle cells (8–13). In contrast to this intrahepatic vasoconstriction, splanchnic arteriolar dilatation exacerbates portal hypertension by increasing portal venous inflow (14–16). Varices develop when the hepatic venous pressure gradient (HVPG), a measurement obtained by transjugular cannulation of the hepatic veins, is elevated >10 to 12 mmHg (17,18). Variceal bleeding occurs when increased variceal vein diameter, decreased wall thickness, and increased intraluminal pressure elevate variceal wall tension beyond the maximum tolerable threshold (16).

Investigators aimed to determine whether clinical benefit could be derived from the ability of β-blockers to reduce portal pressure by reduction of cardiac output (mediated by β1-receptor antagonism), reduction of portal venous flow by unopposed α-receptor-mediated splanchnic vasoconstriction (following antagonism of β2-receptors), and antagonism of the norepinephrine-induced constriction of intrahepatic myofibroblasts, activated stellate cells, and vascular smooth muscle cells (9,10,19–21). Meta-analysis of the several randomized controlled trials (RCTs) undertaken revealed a significant reduction of bleeding rate in patients treated with β-blockers compared to those receiving no treatment or placebo. The beneficial effect was limited to those with medium or large varices and no benefit was seen in patients with small varices (22). However, the bleeding risk of small varices with red wale marks has recently been shown to match that of medium or large varices.

The optimal dose of β-blocker was initially chosen to reduce the heart rate by 25% from baseline or the maximum tolerated dose. Subsequent studies in adults have shown that the extent of reduction of HVPG (by at least 20% of the baseline value, or to an absolute value of <12 mmHg) more strongly indicates the likelihood of successful hemorrhage prophylaxis, whereas heart rate reduction is a poor predictor (23–25).

The advent of EVL as a potential prophylactic therapy was heralded by RCTs in adults in which EVL reduced the incidence of variceal bleeding and mortality by 64%, compared with control patients who received no prophylactic therapy (26). Numerous studies have

been undertaken to compare the efficacy and safety of prophylaxis with β-blockers and EVL. Meta-analyses of all of the studies suggest that EVL is more effective, but when limited to larger studies, each including more than 100 patients, the difference is no longer statistically significant (27). Relative cost-effectiveness, patient tolerance and preference, and effectiveness against other manifestations of portal hypertension (eg, spontaneous bacterial peritonitis) have also been the subject of research studies. While the debate continues, current guidelines for adults state that both interventions are acceptable prophylactic therapy, with β-blockers generally preferred as first-line therapy and EVL reserved for patients in whom β-blockers are contraindicated or poorly tolerated (1).

The search continues for new therapies that are more effective and better tolerated. A recent RCT of carvedilol (a combined nonselective β-blocker and α1-blocker) compared to EVL in 152 patients showed an incidence of first variceal bleed in the carvedilol group of 10%, compared to 23% in the EVL group (28). The study was underpowered, did not include HVPG measurements, and was criticized for a prolonged time from randomization to EVL treatment (27). Therefore further work is required to determine whether this drug offers an improvement over other nonselective β-blockers or EVL. Recent evidence suggests that active angiogenesis may contribute to the development of varices, and studies of animal models suggest a potential future role for antiangiogenic therapy for preventing the complications of portal hypertension (29,30).

VARICEAL HEMORRHAGE IN CHILDREN

Studies from pediatric hepatology referral centers suggest that more than 50% of cirrhotic children have varices (31,32). However, there are no published reports that provide prevalence figures derived from routine screening endoscopies for all of the children with cirrhosis or portal vein thrombosis. It is therefore not clear how many children would need to be screened for a sufficient number of children with varices to be identified for recruitment to a clinical trial. Given that there is no agreement on the utility of primary prophylaxis, it is understandable that there is also no consensus as to whether routine screening endoscopy is indicated for children with cirrhosis or portal vein thrombosis.

There are some reports of the overall number of children who bleed from esophageal varices. Among children with biliary atresia in the first 2 years after portoenterostomy, variceal bleeding occurred in approximately 20% of those who did not require liver transplantation in a study that spanned 1973 to 1992 (33). More recent practice and outcomes are reflected in the combined retrospective experience of the Biliary Atresia Research Consortium, in which 3 variceal bleeds occurred in the first 2 years of life among 104 children with biliary atresia (2.9%), 50% of whom required transplantation during this period (34). In a population-based prospective study of major upper gastrointestinal bleeding, there was 1 annual incidence of portal hypertensive bleeding among 200,000 children (35).

Few studies have examined the incidence of variceal bleeding among children with known varices diagnosed by endoscopy because few centers perform routine screening endoscopy. Likewise, no pediatric data are available on the ability of endoscopic variceal appearance (eg, size, red wales, red spots) to predict future bleeding. However, in 1 South American RCT of injection sclerotherapy for primary prophylaxis of variceal hemorrhage, 42% of children in the control arm experienced esophageal variceal bleeding during 3 years of follow-up (36). Variceal bleeding was also documented to occur in 20% of 12-year-old children during the 2 years after diagnosis of portal vein thrombosis and grade 2 or 3 varices documented at endoscopy (37).

In clinical practice, it is clear that a bleeding episode from esophageal varices is a major clinical event that is associated with significant adverse sequelae, including requirement for blood transfusion and intensive care. Affected children may develop septicemia and ascites and require prolonged admission to the hospital for treatment of these complications. A mortality rate of 19% has been reported within 35 days of variceal bleeding episodes among North American children with liver disease of various etiologies (38). Two other studies showed that 5% and 15% of children with biliary atresia and variceal hemorrhage, respectively, would die (32,39). Interestingly, variceal hemorrhage seems to carry a low risk of death in children with portal vein thrombosis and no parenchymal liver disease (37).

Diagnosis of Varices in Children

Endoscopy is the reference standard for the diagnosis of esophageal varices, but its widespread application has not been implemented due to the lack of evidence for the effectiveness and safety of subsequent therapy to prevent bleeding in children found to have varices. Acceptance of screening endoscopy is poor even by adults with cirrhosis, in which compelling evidence exists for its use, due in part to its invasiveness and the knowledge that more than 50% of cirrhotic adults will be found to have no varices. Interest has therefore arisen in noninvasive tests that may either replace endoscopy or allow better targeting of endoscopy to the highest risk group (40).

A small number of studies in children have suggested that noninvasive tests may identify children with varices with sufficient accuracy to be clinically useful. Such noninvasive tests include the spleen size, the ratio between platelet count and spleen size, and the ultrasound elastography (41–43). Although not yet validated for clinical use, application of these tests within a pediatric clinical trial may help minimize endoscopies in children found to have no varices.

General Issues for Consideration in Designing an RCT of Primary Prophylaxis in Children

To be clear that it is appropriate to undertake a clinical trial of primary prophylaxis in children, there is a need for more data showing the prevalence of varices, the incidence of bleeding, and the associated morbidity and mortality among children from different diagnostic groups and with different variceal or other clinical characteristics.

Children with varices at risk of hemorrhage have multiple different diagnoses and there is a lack of understanding as to the effect the primary diagnosis may have on risk of bleeding and response to prophylactic therapies. There are some data to suggest significant differences in the outcomes of varices due to portal vein thrombosis compared with those due to intrinsic hepatobiliary disease. Inclusion of these 2 patient groups in a single trial should therefore be either avoided or handled appropriately to ensure that meaningful results are obtained that can be generalized into routine clinical practice.

The identification of children for inclusion within a research study of primary prophylaxis will rely on endoscopy, the reference standard for diagnosis of varices. However, the performance of screening endoscopy in children with portal hypertension is not the standard of care due to the absence of evidence that primary prophylaxis is effective in children. Such endoscopy may therefore have to be performed as part of the research protocol, and this raises various issues that are discussed in the section on challenges using EVL within a clinical trial in children.

Scoring systems for the diagnosis and grading of varices during endoscopy have not been validated or standardized in children, and there is little knowledge of their reproducibility. Whether inclusion criteria for a clinical trial were to include assessment of variceal size or appearance needs to be addressed.

Follow-up of any group of children with varices will be complicated by a significant dropout rate due to liver transplantation, portosystemic shunt surgery, and death. Dropout due to these and other reasons may be expected in 20% to 50% of subjects recruited to a study, and sample size should be calculated to allow for this.

PRIMARY PROPHYLAXIS OF VARICEAL HEMORRHAGE IN CHILDREN

Nonselective β-blockers

The description of efficacy and safety of nonselective β-blocker therapy for primary prophylaxis of variceal hemorrhage derives from studies of adult patients who mostly had hepatitis C or alcohol-related cirrhosis. Before considering the use of β-blockers in a clinical trial for the prevention of variceal hemorrhage in children, certain fundamental issues need to be addressed, including the published experience with this therapy in children, the validity in children of the tenets that underlie the use of this therapy, the biological parameters that could be used to determine the appropriate dosing regimen for children, and the effect of potential drug toxicities.

Experience With β-blocker Therapy in Children With Portal Hypertension— There are 6 articles that report clinical experience with the use of β-blockers in children with portal hypertension (44–49), some of which include children undergoing primary prophylaxis (Table 1). The collected experience from these studies involves 131 children who have a variety of etiologies of their underlying liver diseases—none of which is common in adults. Most of the reports are anecdotal in nature and represent descriptions of routine clinical practice. None are formal randomized trials.

The first reported study documented changes in splenic pulp pressure in response to β-blockade; this is the only pediatric analysis assessing portal pressure changes in response to propranolol therapy (44). There are few reports of HVPG measurements in children, and none that measures changes in HVPG in children treated with β-blockers. This is in part because many of the diseases are presinusoidal and may not be amenable to accurate measurement of portal pressure by this approach.

Most of the reported pediatric studies include measurement of reduction in heart rate as a biological response to β-blockade and aim for a 25% reduction from baseline as the optimal response. However, none of the studies elaborates on the practical approaches involved in this complicated assessment in children, for which various challenges are discussed below. The reported propranolol dose provided to achieve "β-blockade" in these studies ranges from 1 to 8 $mg \cdot kg^{-1} \cdot day^{-1}$.

The therapeutic efficacy of β-blockers cannot be determined from these published pediatric studies, particularly because there are no data presented from relevant control groups. Among the children with variceal bleeding while receiving β-blocker therapy, there are no reports of catastrophic consequences of that bleeding. This has been a concern for some clinicians because, compared with adults, children are more dependent upon chronotropy for maintenance of systemic blood pressure during hypovolemia. The prevalence of adverse events is low in the published reports, although systematic investigation of potential toxicities is unlikely to have been undertaken.

Overall, one can surmise from the published experience that propranolol has been used anecdotally in children with portal hypertension, dosing regimens may need to be highly individualized, and the treatment appears to be relatively safe.

Hyperdynamic Circulation in Pediatric Portal Hypertension—There are almost no data that have been published regarding this important aspect of the pathophysiology of portal hypertension in children. Certainly, the hyperdynamic circulation has not been well described in children with portal hypertension. Preliminary investigations in infants suggest that the hemodynamic changes in portal hypertensive children may be different from those in adults, although further research is required (50). Thus, at present, there are inadequate data to determine whether the hemodynamic pathophysiology in children with portal hypertension is similar to adults such that the further investigation of β-blocker therapy in children is appropriate.

Biological Response to Guide β-blocker Dosing in Children—It is sometimes assumed that a reduction in heart rate of 25% would indicate adequate dosing of β-blockers for children with portal hypertension. However, challenges are raised by the age-dependent physiological variation of normal heart rate in children and the interpretation of heart rate data in children with various states of activity and anxiety. Clinicians who care for young children know the inherent difficulties in documenting a “resting” basal heart rate in a child in a typical clinical setting.

Alternative measures of appropriate dosing may include 24-hour ambulatory heart rate monitoring (eg, Holter monitoring) or measurement of propranolol levels in blood. Interestingly, clinicians who manage children with hypertrophic cardiomyopathy with β-blockers aim to minimize beat-to-beat variability in heart rate, rather than a target reduction in mean heart rate, which may require between 5 and 23 $mg \cdot kg^{-1} \cdot day^{-1}$ and correlate with serum propranolol levels between 200 and 900 μg/L (51). These high doses of propranolol were reportedly well tolerated by the children.

Toxicities—The potential toxicities of β-blocker therapy would need to be considered and monitored in the context of a formal clinical trial. Relevant and potentially problematic issues include reactive airway disease, impaired exercise tolerance, risk of hypoglycemia, behavioral issues, and potential risks associated with hypotension in the setting of rapid blood loss.

Challenges Using β-blockers in a Pediatric Clinical Trial—Approval from regulatory authorities will be required for the clinical investigation of propranolol in children because it is not approved for use in the management of portal hypertension and has not been approved for use in children. Propranolol and its equivalents are not under patent protection and industry interest in investigating these compounds is likely to be limited. Applications would therefore be required to granting agencies for the considerable funding required for a large multicenter clinical trial. The justification for and design of a clinical trial, and thus the success of applications for funding, would be enhanced by results from research that addresses the high-priority areas listed below.

Double blinding is considered impossible in trials of non-selective β-blocker therapy because patients receiving these drugs are usually aware of adverse effects, such as exercise intolerance. Blinding of the investigators can be maintained only with an elaborate system to ensure that physicians who manage dose changes or adverse effects are separate from those determining study endpoints, which may be impractical in many centers. The choice of objective endpoints is therefore of critical importance to avoid bias. Assessment of reported endpoints at a remote site by blinded investigators within the context of a multicenter study would also help reduce bias.

Endoscopic Variceal Ligation in Children

Following the early descriptions of its use in children, EVL rapidly replaced injection sclerotherapy as the endoscopic treatment of choice for secondary prophylaxis after an initial variceal hemorrhage in a child. Its widespread use was encouraged by the development of multiband appliances that did not require repeated removal and repassage of the endoscope and by the recognition that the devices could be used even in small children, down to approximately 12 to 15 kg body weight. The use of EVL in preference to injection sclerotherapy was supported by the results of an RCT, in which band ligation was more effective and safer than sclerotherapy for secondary prophylaxis of variceal bleeding in children (52). A number of other nonrandomized trials have reported the use of EVL for secondary prophylaxis, even in small children, with few complications and a recurrent bleeding rate of <5% (53).

There have been a small number of nonrandomized trials of band ligation for primary prophylaxis of esophageal variceal hemorrhage in children (Table 1). These have shown band ligation to be well tolerated by children, with a low subsequent bleeding rate and no reports of major complications. To date there has been only 1 RCT of pediatric endoscopic primary prophylaxis (36). This study compared children who received injection sclerotherapy with a control group that received no treatment and showed a 50% reduction in the risk of variceal bleeding in a 4-year period, but with no effect on mortality.

The published experience therefore suggests that EVL is a valid therapeutic option to explore further within an RCT for primary prophylaxis of variceal hemorrhage in children.

A Pilot Study of EVL in Children—In 2006, 3 pediatric hepatology centers in the United Kingdom agreed to undertake a pilot study of such a trial. This pilot study is ongoing, and therefore its results have not yet been reported in full. Children are included if they are <17 years old, have large esophageal varices found at a screening endoscopy, with no history of previous bleeding, and for whom endoscopic variceal ligation is feasible (usually judged by a weight >12–15 kg). Exclusion criteria include pharmacological therapy for prophylaxis against variceal bleeding within the previous 6 months and the anticipated need for liver transplantation or portosystemic shunt within 6 months of recruitment. A standardized protocol for EVL and follow-up surveillance endoscopy was applied across all of the participating centers.

Valuable early experience has been gained from this study. The overall enrollment rate is approximately 50% of families approached for inclusion. Recruitment has been greatest in those centers with the most research nursing support. One third of those undergoing screening endoscopy have been found to have varices that meet the inclusion criteria. Patients and families have found the number of endoscopies challenging and the protocol has therefore been modified to decrease the frequency of surveillance endoscopy following initial ablation of varices. So far, bleeding has occurred in 1 of 6 patients recruited into the control arm and in none of the treated patients.

Challenges Using EVL in a Pediatric Clinical Trial—As discussed above, screening children with portal hypertension for varices using endoscopy is not the standard of care and the screening and subsequent follow-up endoscopies are therefore likely to be included as research procedures (rather than clinically indicated procedures) within a future clinical trial. There are several clinical practice, ethical, and financial challenges that would need to be overcome if endoscopy and EVL are included in a clinical trial protocol.

The most appropriate follow-up schedule to achieve successful primary prophylactic EVL in children is unknown, including the frequency of repeat EVL procedures, the need to modify

this frequency on the basis of variceal size or appearance, and the endpoint at which further EVL procedures are discontinued. Data from pilot or phase 2 studies such as those described above may help define the approach that is most likely to be effective. Once the ideal approach is known, challenges in achieving adequate recruitment and compliance with this approach within a research study may remain. In the pilot study described above, for example, the enrollment rate was only 50% and the follow-up endoscopy schedule was changed during the course of the study in response to difficulties that families were facing with regard to compliance.

In most cases, children require either sedation or general anesthesia to undergo endoscopy. The provision of such care to children for research purposes will have considerable financial cost and will require specific arrangements for staffing and scheduling at each participating health care facility.

Maintenance of blinding of the research subjects to the treatment provided to them clearly would be impossible. As with a study of β-blockers, the choice of objective endpoints would be essential, and a system to blind the investigators who assess outcomes would further help reduce bias.

The ethical implications of undertaking endoscopy and EVL under sedation or general anesthesia in children for research purposes would need to be considered by local institutional review boards (IRBs) within the usual reference framework. The Code of Federal Regulations, part 46 (Protection of Human Subjects), from the US Department of Health and Human Services, is used as a guide for IRBs. The code addresses the situation in which a research intervention or procedure involves more than minimal risk for a child research subject and does not hold out the prospect of direct benefit for the individual subject (54). The code suggests that such a research intervention is justifiable if the risk represents a minor increase over minimal risk, the intervention presents experiences to the research subject that are reasonably commensurate with the expected medical and psychological situation, the intervention is likely to yield generalizable knowledge of vital importance for the understanding or amelioration of the subject's condition, and adequate provision is made for soliciting assent of the children and permission of their parents or guardians. Therefore, a valid argument could be put to IRBs that endoscopy is justifiable within a clinical trial of primary prophylaxis, although each IRB would then be required to consider its response to such an argument.

Investigators would need to be satisfied that the benefits of primary prophylaxis for children are unclear before embarking on a research study whose control group receives no effective therapy. Some investigators may have already introduced primary prophylaxis into their approach to routine clinical care and would need to be willing to discontinue this approach for patients enrolled in the control arm of a trial of either β-blockers or EVL. There is equipoise as to the risks and benefits of primary prophylaxis for children with varices in our opinion, which is based on the evidence and issues discussed here, especially the lack of RCTs in children, the inconclusive, uncontrolled case series, and the considerable uncertainty surrounding the extrapolation to children of the results of studies in adults.

SAMPLE SIZE CONSIDERATIONS

If a clinical trial of primary prophylaxis in children is to be planned, then the feasibility of the trial depends in part upon the required sample size. Sample size estimates are based on the desired power of the study, the acceptable type 1 error rate, and the anticipated magnitude of the treatment effect. Thus, estimates of sample size for a clinical trial are determined by the study design and dictated by the desired results. Study scenarios in which

the primary outcome measure is either a categorical or continuous variable are considered below.

Categorical Primary Outcome Variable

The primary outcome chosen for a primary prophylaxis trial may be the percentage of subjects who have experienced variceal hemorrhage by the end of a fixed, predetermined, follow-up period (a categorical outcome variable). The primary analysis would be a comparison of proportions (percentage experiencing a bleed in treated vs nontreated groups). Usually, regardless of the study, we desire a power of 0.8 and elect to accept a type 1 error (false-positive or “alpha”) of 0.05. The duration of follow-up observation, however, is explicitly determined by the study design (in this example, we choose 2 years). The proportion of the study control group who will bleed within this time frame can be predicted from the results of previous studies, and although often thought to be “fixed,” it is determined in part by the inclusion and exclusion criteria (eg, the occurrence of bleeding in the control group may be higher in a study that includes only patients with the largest varices). For this example, we assume 25% of control subjects would be expected to bleed within 2 years of enrollment.

The investigators must then choose the smallest effect size that they consider being clinically important and that they would not want the study to miss. For example, they may consider it important to be able to show a reduction in bleeding during 2 years of follow-up from 25% in the control patients to 15% in the treatment group, which is an absolute risk reduction (ARR) of 10%. In this situation, with alpha set at 0.05 and power at 0.8, they would require a sample size of 250 patients in each group (total sample size 500). If fewer patients are recruited to the study, then there may be insufficient power to demonstrate that an ARR as small as 10% is present. However, if they wished to be able to demonstrate an ARR no smaller than 12.5%, which at half the control rate is a relative risk (RR) of 2, then the required sample size would only be 152 patients in each arm (total sample size 304). If the duration of follow-up were extended to 3 years, then the expected control group bleeding rate would be increased from approximately 25% to, we shall assume, 38%. If the other conditions described above remain the same and they sought to still show a RR of 2, then the required sample size would be further reduced to 87 in each arm (total sample size 174). Thus, a trial’s inclusion and exclusion criteria (through their effect on the bleeding rate in the control group) and its duration of follow-up both have important potential effects on the required sample size.

Continuous Primary Outcome Variable

If the primary outcome variable in a clinical trial of primary prophylaxis were the duration of follow-up before variceal hemorrhage occurred (“time to event” or TTE), then this would be a continuous outcome variable. The primary analysis would be a survival analysis. In this situation, the alpha error and power should remain the same as before (0.05 and 0.8, respectively). In this style of analysis, sample size is mitigated by the median TTE for controls, and the minimum duration of follow-up recorded for all of the participants. Again, the median TTE in the control group is essentially “fixed,” although it may be changed depending on the inclusion criteria as discussed above. The follow-up period, however, depends solely upon study design and may be manipulated by varying both the duration of the recruitment phase and the period of additional ongoing follow-up once recruitment is complete. Once again, the investigators must choose the minimum effect size that they consider important and do not want the study to miss. The effect size can be expressed either as a median TTE for cases or as a hazard ratio comparing cases to controls. In short, the hazard ratio is the relative risk of the event occurring given that it has not yet occurred.

For example, if the median TTE among controls is 4 years, in a trial in which recruitment will occur for 2 years, with each child followed for a minimum of 2 additional years, if the minimum effect size of interest is a hazard ratio of 2 (ie, the median TTE in the treatment group is 8 years), the required sample size is 112 children in each arm (total sample size 224). Changes in the recruitment period and different median TTE in controls will bring about changes to the required sample size.

Variceal Hemorrhage in the Control Group

Achieving a realistic sample size for a future clinical trial therefore depends in part on the selection of children with a high risk of variceal bleeding. Current knowledge of the bleeding risk associated with varices of different sizes and appearances in children is inadequate. In adults, clinical predictors of variceal hemorrhage include the severity of liver disease measured by the Child-Pugh score, the presence of ascites, the size and appearance of the varices at endoscopy, and the degree of elevation of HVPG (55). The role of similar variables in predicting variceal bleeding in children is unknown. Preliminary data suggest that noninvasive tests may help to predict variceal bleeding in children, and thus may help the selection of high-risk children for future research studies (56). However, further studies are required to validate these early results and to examine the effect on the risk of variceal hemorrhage of noninvasively measured variables, including the presence of ascites, degree of splenomegaly, abnormalities identified by imaging studies, indirect measures of liver fibrosis.

Population Requirements for a Clinical Trial

The total population of children required to support a clinical trial can be estimated if we assume that 1 in 200,000 children experience a variceal bleed each year (35), the study design requires 150 children in each arm, 25% of subjects who receive no intervention experience variceal bleeding (ie, the control group bleeding rate is 25%), 50% of potentially eligible subjects agree to take part in the study, and the dropout rate is 20% (due to, eg, liver transplantation, death, subject choice, adverse effects). The childhood population required to support such a trial would be approximately 36,400,000, which is about half the children in the United States. The size of this population could be changed by the techniques discussed above, for example, by extending the recruitment and follow-up periods, but the number of study centers to achieve an adequate sample size will remain considerable and may ultimately require a multinational, multicenter study.

A FRAMEWORK FOR FUTURE INVESTIGATIONS

There is a need for further research to provide important information on which to base the design of a clinical trial of primary prophylaxis of variceal hemorrhage in children and to help overcome many of the barriers to the successful completion of such a trial (Table 2). Undertaking a trial before these additional research questions have been answered would be premature. High-priority areas for research are as follows:

1. The natural history of varices in children with various underlying causes of portal hypertension, including the incidence of variceal hemorrhage and the associated morbidity and mortality
2. The diagnosis of varices in children, including the use of noninvasive tests and the reproducibility of interpretation of endoscopic appearances
3. The accurate identification of children at high risk of variceal bleeding
4. Description of the hemodynamic status of children with portal hypertension and the effect of nonselective β-blockers on this

5. Appropriate dosing of nonselective β-blockers in children to optimize the effect on portal pressure and the development of biomarkers or other measures to determine optimal dose provision in an individual child
6. The development and validation in children of biomarkers that indicate an adequate response to prophylactic therapy, such as HVPG or noninvasive tests of portal or variceal blood flow
7. The most effective approach to EVL in children, including frequency of repeat EVL sessions and endpoint for return to routine screening frequency
8. Development of multicenter registry-based research techniques and propensity scores to provide an alternative approach to estimating the efficacy of prophylactic therapies in children

CONCLUSIONS

It has been more than 25 years since the pharmacological prevention of variceal hemorrhage in adults was first demonstrated. Unfortunately, the lack of RCTs in children still precludes evidence-based recommendations for the prophylactic management of children at risk of variceal hemorrhage. Although 2 interventions (nonselective β-blockers and EVL) that are of proven efficacy in cirrhotic adults could be the subject of clinical trials in children, additional research is required to provide the information needed to design such a trial and to determine whether it is feasible. The sample size calculations, cost implications, and ethical challenges presented here suggest that the practical likelihood of successful completion of such a trial is minimal. Alternative approaches to determining the efficacy of primary prophylactic interventions should therefore be developed.

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TABLE 1

Published studies of primary prophylaxis in children

	Design	n	Follow-up	% Bleeding
β-Blockers				
Shashidhar et al (46)	CS	17	3 y	35
Ozsoylu et al (47)	CS	45	5 y	16
Erkan et al (49)	CS	10	5.2 y	10
EST				
Paquet (57)	CS	2	10 y	0
Howard et al (58)	CS	17	2.5 y	0
Maksoud et al (59)	CS	26	2.4 y	42
Goncalves et al (36)	RCT	100	4.5 y	6% EST vs 42% control
Duché	CS	13	8 mo	8
EVL				
Cano et al (60)	CS	4	Not given	0
Sasaki et al (61)	CS	9	23 mo	10
Celinska-Cedro et al (62)	CS	37	16 mo	0

CS = case series; EST = endoscopic sclerotherapy; EVL = endoscopic variceal ligation; RCT = randomized controlled trial.

TABLE 2

Summary of the barriers to undertaking a clinical trial of primary prophylaxis in children

General barriers	Poor understanding of natural history and consequences of variceal hemorrhage
	Multiple etiologies of underlying portal hypertension in children
	Undertaking diagnostic endoscopy under sedation or anesthesia within a research protocol with uncertain benefits for the individual child
	No validation in children of scoring systems for the endoscopic appearance of varices
	Expected high dropout rate from research protocol
	Large sample size requirement
Barriers to a trial of β-blockers	Inadequate understanding of hemodynamic pathophysiology in children with portal hypertension
	Inadequate understanding of appropriate dosing of β-blockers in children with portal hypertension
	Drug toxicity
	Difficulty in maintaining double blinding
	Requirement for regulatory approval
	Funding from industry unlikely
Barriers to a trial of EVL	Poor acceptance of endoscopy by children and/or families, leading to low recruitment rate
	Poor compliance with repeat endoscopies
	Inadequate knowledge of optimal schedule for follow-up EVL in children
	Undertaking interventional endoscopy under sedation or anesthesia within a research protocol with uncertain benefits for the individual child
	Impossible to maintain double blinding

EVL = endoscopic variceal ligation.