

Recent Trends in the Endoscopic Management of Variceal Bleeding in Children

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Variceal bleeding results in significant morbidity and mortality in both children and adults. The guidelines for the management of variceal bleeding are well established in adults but not in children as there have been insufficient pediatric studies of this disorder. In addition, the adult guidelines for treatment of variceal bleeding cannot be applied directly to children as the etiology and natural course of this disease differs between children and adults. Examples of recommended treatments in children include endoscopic variceal ligation as secondary prophylaxis for biliary atresia whereas a meso-Rex shunt operation for extrahepatic portal vein obstruction. In this review, we discuss prophylaxis options and some technical aspects of endoscopic management for variceal bleeding in children. (**Pediatr Gastroenterol Hepatol Nutr** 2013; 16: 1~9)

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INTRODUCTION

Variceal bleeding is one of the most serious complications of portal hypertension in children and adults alike [1-3]. Portal hypertension is an increase in portal vein pressure and is directly determined by both the blood flow through the portal system and the vascular resistance to that flow. At an anatomic level, this can result from a disturbance of hepatic vein outflow, liver disease, and portal vein obstruction. The mesenteric and splenic veins unite to drain into the portal vein. An increase in portal pressure induces the development of collaterals such as the gastroesophageal

vein, left gastric vein, splenorenal vein, and eventually the occurrence of esophageal and gastric varices [4].

The etiologies of portal hypertension have revealed that biliary atresia is its most common cause followed by extrahepatic portal vein obstruction (EHPVO) [2,5,6]. A relatively higher incidence of biliary atresia is observed at our institution as it is a large liver transplantation center. There are sufficient studies on adults in support of the clinical importance of variceal bleeding. Most of the underlying causes in adults are the result of liver cirrhosis. Approximately 50% of patients with cirrhosis consistently show varices.

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Variceal bleeding occurs in about one third of these cases, rebleeding in 70%, and death results from variceal bleeding in up to 30% of affected patients [3]. A consensus for the management of portal hypertension has been built at various conferences using evidence-based guidelines which are well established in adults. The most recent of these was the Baveno V meeting held in 2010 [7].

In contrast to the situation in adults however, there have been far fewer studies of variceal bleeding in children, in whom the etiology of this disorder differs from adults. The most common causes in children are biliary atresia and EHPVO in contrast to liver cirrhosis in adults. Therefore, the natural course of variceal bleeding is also different from adults. Children with variceal bleeding show a relatively lower mortality of less than 10% [2,3,8-11] than adults where it can reach up to 30% [3]. However, one third of the deaths from biliary atresia before liver transplantation became available were caused by variceal bleeding [12]. In a recently well designed study of biliary atresia following a Kasai operation by Duché et al. [13] it was found that 70% of the patients had varices and 20% developed variceal bleeding early after surgery. Hence, variceal bleedings in children is also a significant issue for which management strategies that differ from those in adults are necessary. However there is no evidence based guideline in children, instead there are two expert pediatric opinions based on adult Baveno guideline which took place in 2006 [14] and 2012 [15].

We here review the endoscopic management of variceal bleeding in children based on existing reports, including the treatment of acute variceal bleeding cases and the prophylactic strategies for the prevention of future bleeding. We also briefly discuss some technical aspects of endoscopic treatment.

MEASUREMENT AND DEFINITION OF PORTAL HYPERTENSION

The significance of measuring portal venous pressure is that it can estimate the current status of the patient and also evaluate the response to treatment.

However, the direct measurement of the free portal pressure requires an invasive intraoperative approach. The hepatic venous pressure gradient (HVPG) is a measure of the gradient between the wedged and free hepatic vein pressure [16] and is a less invasive transjugular approach. It also can be performed during a trans-jugular liver biopsy.

The normal HVPG is less than 5 mmHg and an increase above this level indicates that portal hypertension has developed. If the HVPG measures above 10 mmHg, varices will develop. Variceal bleeding usually occurs when this pressure is more than 12 mmHg. Thus, the prevention of bleeding is achievable the HVPG can be controlled below 12 mmHg. Most of these findings have been reported from adult studies. The measurement was also feasible in children [17], but the number of pediatric studies is currently not sufficient.

PRE-PRIMARY AND PRIMARY PROPHYLAXIS

Pre-primary prophylaxis denotes the preventive management of the development of varices. It is recommended that all cirrhotic adult patients should be screened for varices when diagnosed. However children with portal hypertension should only be screened by surveillance endoscopy if they are candidates for primary prophylaxis or for specific counseling related to lifestyle. If considering surveillance endoscopy, variables such as thrombocytopenia, splenomegaly, and albumin level help to determine the likelihood of varices and to triage for endoscopy [18]. Animal studies have shown that propranolol has preventative effects on the formation of varices [19]. However, a previous clinical study in adult cirrhotic patients found no effects of this beta-blocker [20]. It is not therefore recommended at present to use non-selective beta-blockers (NSBB) to prevent the formation of varices either in adults [7] or children [21].

Primary prophylaxis is intended to prevent the first episode of variceal bleeding in an individual who has varices and has not experienced variceal

bleeding previously. In adults with medium to large sized varices, prophylaxis with beta blockers or band ligation is recommended [7]. In children however, studies of primary prophylaxis are insufficient to make any definitive treatment recommendation (Table 1). Most studies of sclerotherapy in children have been case series. Even the number of studies on the use of NSBB is also lacking in children. In 2000, Gonçalves et al. [22] reported in their randomized controlled study that sclerotherapy is effective as a primary prophylaxis for variceal bleeding. However as there is also an increasing incidence of gastric varices and portal hypertensive gastropathy bleeding, further studies are needed to provide treatment guidelines for these cases. The general use of primary prophylaxis is thus not recommended in children because sufficient data are lacking. Prophylactic therapy with endoscopic band ligation (EBL) only may be considered in some children within defined clinical circumstances with an ongoing evaluation of outcomes [21]. The long-term use of NSBB is also not recommended in children due to the lack of sufficient data because these agents can block the physiologic compensatory mechanism for hypervolemia when bleeding occurs.

Duché et al. [13] have previously studied 138 children with biliary atresia and analyzed the risk factors for the occurrence of a first episode of variceal bleeding. In that study, moderate to large sized varices had a higher risk of bleeding; grade 0 and 1 vari-

ces lower than 25% risk, whereas grade 2 and 3 showing the higher incidence of bleeding during follow-up. These authors reported that the presence of a red color sign, gastric varices, and portal hypertensive gastropathy was also associated with an increasing incidence of variceal bleeding in their patient cohort. In our previous study, reported in the Annual Meetings of the Korean Pediatric Society [22], we found that one third (9 out of 28) of the children we analyzed developed a first episode of variceal bleeding within six months of diagnosis. The size of the varices and the presence of gastric varices were found to be risk factors for this occurrence. Hence, primary prophylaxis can be considered in selected children with medium to large varices and who also show evidence of red color sign, gastric varices, or portal hypertensive gastropathy. In terms of the method of prophylaxis, only band ligation is currently recommended in children [15].

MANAGEMENT OF ACUTE VARICEAL BLEEDING

A detailed review of the management of acute variceal bleeding is described elsewhere [15]. Management of this disorder should commence by securing the IV line access and the resuscitation of fluid in the ICU. Overtransfusion should be avoided and coagulation abnormalities should be corrected if necessary. Thereafter, the management strategy should

Table 1. Primary Prophylaxis of Variceal Bleeding in Children

Reference	Type of study	Number of patients	Disease	Intervention	Variceal bleeding (%)
Shashidhar et al. [24] (1999)	Case series	17	Both	Propranolol	35
Ozsoylu et al. [25] (2000)	Case series	45	Intrahepatic	Propranolol	16
Howard et al. [9] (1988)	Case series	17	Both	EST	0
Maksoud et al. [8] (1991)	Case series	26	Both	EST	42
Gonçalves et al. [21] (2000)	RCT	100	Both	EST	6 EST, 42 control
Itha and Yachha [26] (2006)	Case series	163	Extrahepatic	EST	7
Duché et al. [27] (2008)	Case series	13	Intrahepatic	EST	8
Maksoud-Filho et al. [28] (2009)	Case series	32	Extrahepatic	EST	0
Sasaki et al. [29] (1998)	Case series	9	Intrahepatic	EBL	10

Both: both intra- and extra-hepatic, EST: sclerotherapy, RCT: randomized controlled trial, EBL: endoscopic band ligation. Modified from Molleston. *J Pediatr Gastroenterol Nutr* 2003;37:538-45, with permission [23].

focus on stopping the variceal bleeding. Octreotide should be administered at the time of admission and continued for five days thereafter once the variceal bleeding is under control. Endoscopic evaluation and management should be performed as soon as possible and certainly within 24 hours of admission. For the endoscopic management of acute esophageal variceal bleeding, band ligation is recommended in the first instance, otherwise sclerotherapy is recommended for both adults and children. If the above management approaches fail to stop the bleeding, a balloon tamponade can be attempted. Thereafter, radiologic and surgical treatments should be applied.

There have been many randomized controlled trials (RCTs) in adults that have compared variceal band ligation with injection sclerotherapy in the control of acute esophageal variceal bleeding [30,31]. These data indicate that band ligation is not less effective than sclerotherapy and produces fewer occurrences of procedure-related complications such as procedure related perforation, bleeding, ulceration, and stricture formation at the injection site. In the case of children (Table 2), and in contrast to adult studies, RCTs are lacking and even when they have been undertaken, the sample sizes have been too small. With these limited results, we can conclude that octreotide is effective in controlling variceal bleeding in a significant number of patients and that endoscopic therapy with band ligation or injection sclerotherapy can be done

[15]. We previously performed band ligation in 40 children and sclerotherapy in 17 children as an initial mode of therapy [22]. Our current retrospective study may have a selection bias because we performed band ligation first unless it was not feasible for younger children in which case we performed sclerotherapy. Even with these limitations however, our present study shows that both band ligation and sclerotherapy have a relatively higher rate of therapeutic success (around 90%) in controlling acute bleeding episodes. We found no differences in the incidence of complications between these two treatments. Complications that did arise were all relatively minor such as fever and abdominal pain. A perforation developed in only one child who received band ligation.

For the endoscopic treatment of gastric variceal bleeding in adults, vascular occlusion with N-butyl-2-cyanoacrylate injection is recommended because sclerotherapy has shown a high rate of complications [32] and band ligation shows a lower rate of therapeutic success and higher rate of rebleeding than vascular occlusion in these cases [33]. For children, even though vascular occlusion may be considered, the number of studies on N-butyl-2-cyanoacrylate injection of children in the management of gastric varices is too small to properly evaluate this treatment modality in pediatric cases. Radiologic and surgical treatments are instead recommended [15]. In our previous assessment of 11 children who received

Table 2. Management of Acute Variceal Bleeding in Children

Reference	Type of study	Number of patients	Disease	Intervention	Control of bleeding (%)
Tuggle et al. [35] (1988)	Case series	15		Vasopressin	60
Siafakas et al. [36] (1998)	Case series	4	Intrahepatic	Octreotide	100
Lam et al. [37] (2001)	Case series	2	Both	Octreotide	50
Sarin et al. [11] (1988)	Case series	10	Both	EST	100
Sokal et al. [1] (1992)	Case series	18	Intrahepatic	EST and somatostatin	94
Sasaki et al. [29] (1998)	Case series	2	Intrahepatic	EBL	100
Moon et al. [38] (2000)	Case series	9	Both	EBL	78
McKiernan et al. [39] (2002)	Case series	10	Both	EBL	100
Zargar et al. [40] (2002)	RCT, EBL vs. EST	49	Extrahepatic	Octreotide, EBL/EST	64 100 (4/4)
Oh et al. [22] (2011)	Non-RCT	57	Both	EBL vs. EST	89 EST, 90 EBL

Both: both intra- and extra-hepatic, EST: sclerotherapy, EBL: endoscopic band ligation, RCT: randomized controlled trial. Modified from Molleston. *J Pediatr Gastroenterol Nutr* 2003;37:538-45, with permission [23].

an N-butyl-2-cyanoacrylate injection [32,34], we found that we could control the gastric variceal bleeding in 80% of these patients, but that a higher rate of relapse (50%) occurred. Severe complications, such as distant embolism and bacteremia, did not occur in these children as a smaller injection volume was applied than that recommended in adults. Our previous study thus suggested that vascular occlusion with N-butyl-2-cyanoacrylate is feasible in children with gastric variceal bleeding. Further studies will however be needed.

SECONDARY PROPHYLAXIS

In the prevention of variceal re-bleeding, which is a secondary prophylaxis in adults, NSBB, sclerotherapy and EBL have all been found to decrease the risk this occurring [7]. A recent study has shown that a combination of NSBB and band ligation is the best treatment regimen for adults [41]. Otherwise, radiological and surgical shunts should be considered [7]. Most of the studies of secondary prophylaxis in children are case series (Table 3). Even in these studies, endoscopic treatment is suggested to reduce the rate of bleeding recurrence more effectively than his-

torical control measures. Zargar et al. [40] previously performed an RCT of the efficacy of band ligation and sclerotherapy in children and found that band ligation showed a higher efficacy. Two subsequent comparative studies also reported that band ligation is more effective and produces fewer complications [42,43].

Two alternative methods of secondary prophylaxis for variceal re-bleeding are needed in children, one for liver cirrhosis such as biliary atresia and the other for EHPVO. In pediatric cirrhosis cases, band ligation is currently the best treatment method. If band ligation is not feasible in these children, sclerotherapy is recommended. Even though the use of NSBB can be used to prevent rebleeding, it should be considered in children only when band ligation and sclerotherapy cannot be applied [15]. Unless endoscopic treatments are effective, surgical shunting, transjugular intrahepatic portosystemic shunt, liver transplantation (especially for decompensated liver cirrhosis [LC]) should be considered as treatment options.

Due to the recent development of a physiologic intrahepatic shunt operation, the meso-Rex shunt, approaches to the management of children with

Table 3. Secondary Prophylaxis of Variceal Bleeding in Children

Reference	Type of study	Number of patients	Disease	Intervention	Bleeding (%)
Shashidhar et al. [24] (1999)	Case studies	4	Intrahepatic 75%	Propranolol	25
Ozsoylu et al. [25] (2000)	Case series	15	Intrahepatic	Propranolol	53
Howard et al. [9] (1988)	Case series	108	Intrahepatic 67%	EST	39 early, 13 late
Sarin et al. [11] (1988)	Case series	31	Intrahepatic 39%	EST	16
Hill and Bowie [45] (1991)	Case series	32	Intrahepatic 25%	EST	38 early, 7 late
Maksoud et al. [8] (1991)	Case series	62	Intrahepatic 72%	EST	45 early, 15 late
Sokal et al. [1] (1992)	Case series	19	Intrahepatic	EST	33 early
Karrer et al. [46] (1994)	Case series	7	Extrahepatic	EBL	14 early
Stringer and Howard [5] (1994)	Case series	36	Extrahepatic	EST	31
Price et al. [47] (1996)	Case series	22	Intrahepatic 64%	EBL	27 early, 23 late
Yachha et al. [10] (1997)	Prospective series	50		EST	26 early, 0 late
Maksoud-Filho et al. [28] (2009)	Case series	50	Extrahepatic	EST	60
Fox et al. [48] (1995)	Case studies	7	Intrahepatic	EBL	29
McKiernan et al. [39] (2002)	Prospective series	28	Intrahepatic 71%	EBL	8
Zargar et al. [40] (2002)	RCT	49		EBL vs. EST	25 EST, 4 EBL
Poddar et al. [42] (2011)	Prospective series: comparative analysis	161	Extrahepatic	EST vs. EBL+EST	11 vs. 4

EST: sclerotherapy, EBL: endoscopic band ligation, RCT: randomized controlled trial. Modified from Molleston with permission [23].

EHPVO which comprises a comparable number of etiology especially for the children is different from those with LC [44]. In terms of the acute management of variceal bleeding, endoscopic management remains the first choice. For prophylaxis, the meso-Rex shunt is now the primary recommendation. This procedure is well described elsewhere [44]. Five children with EHPVO in our hospital have been treated with a meso-Rex shunt with satisfactory patency (unpublished data).

TECHNICAL ASPECTS OF ENDOSCOPIC MANAGEMENT

EVL can stop variceal bleeding through rubber band ligation of the variceal vessel i.e. mechanical strangulation [49,50]. After confirming the target varices that require ligation, the ligation device is put onto the tip of an endoscope and directed toward the surface of variceal columns to be ligated, then suck the variceal vessel into device, then the band should be fired when the red-out occurs. Banding should start at just above the gastroesophageal junction and this should be followed by upward and spirally banding of another varix. There are two types of ligation device that can be undertaken in this way, single band and the multiple bands. A lately developed multiple band ligator can eliminate the need for repeated introduction of the endoscope [39], and therefore it does not need an overtube which reduces the banding time. However, because the multiple ligator has a larger diameter, it cannot be readily used in a small child. In fact, even a single ligator may not be feasible to use in a young child. In cases of bleeding from esophageal varices, band ligation needs to be applied as soon as possible and then repeated every 2 to 4 weeks until the varices are fully eradicated. Two to 4 sessions in total are usually required for the eradication of esophageal varices and the formation of circumferential scars at the distal esophagus.

The hemostatic mechanism underlying injection sclerotherapy is an intravariceal thrombosis caused by the sclerosant which later results in an ulcer and fibrosis [51]. In addition, paravariceal injections can

cause edema in the surrounding tissues and compress the variceal vessel and later induce inflammation and fibrosis. These effects cause the disappearance of varices. Significantly, whereas a band ligation device can only be used with an adult endoscope, an injection needle can be applied to every scope. Hence, sclerotherapy can be performed using a small endoscope and be applied even to a neonate. It is also a very inexpensive method and is not technically difficult.

In contrast to sclerosant, N-butyl-2-cyanoacrylate forms into a hard plastic acryl when it comes into contact with water or blood. The intravariceal injection of this compound therefore causes rapid occlusion of the varices when it makes contact with blood [52]. To prevent damage in the working channel when applying this method, the radiographic contrast agent lipiodol is mixed with the N-butyl-2-cyanoacrylate to delay permanent hardening and enable radiologic observations after the procedure. If the N-butyl-2-cyanoacrylate is too dilute to travel through the vessels due to slow hardening, there is a risk of a fatal cerebral or pulmonary embolism developing. Small aliquots are thus recommended for these injections. When used in small children, even for the treatment of a gastric varix, we have in the past uses a very small aliquot (0.3 mL) of a thicker mixture of N-butyl-2-cyanoacrylate [34]. We recommend a repeat of this injection after four days in pediatric cases.

CONCLUSION

The management of variceal bleeding in children is a challenging and less well established treatment modality due to a dearth of good evidence that can be used to evaluate the risk and benefits of a particular strategy. Currently, endoscopic band ligation is the primary choice for the management of variceal bleeding in children. However, this treatment cannot be applied to young and small children due to technical limitations and sclerotherapy is still recommended as an alternative approach in these cases. Primary prophylaxis is only indicated in some children and secondary prophylaxis is recommended for cirrhotic children, whereas a meso-Rex shunt operation is the first

choice for prophylaxis in children with EHPVO. Many of the current recommendations for the management of variceal bleeding have been adopted from case series in children and RCTs in adults. However, portal hypertension in children has a different etiology and natural course than in adults and RCTs in children need to be performed to provide an appropriate evidence base for the future treatment and management of pediatric cases of variceal bleeding.

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