

## Original Articles

# Endoscopic Treatment of Gastroesophageal Varices: Efficacy and Safety in Children

JP LU, Y HUANG, SY CHEN, J WU

### Abstract

**Purpose:** Our purpose was to evaluate the efficacy and safety of endoscopic variceal band ligation (EVL) and Histoacryl injection for the treatment of gastroesophageal varices in children. Risk factors of rebleeding were analysed preliminarily. **Methods:** 15 children with esophageal varices and/or gastric varices who received EVL and/or Histoacryl injection were enrolled at our endoscopy center between October 2009 and March 2012. Demographic data, clinical characteristics and endoscopic data were registered and analysed as a Single-center prospective study. **Results:** The mean age was  $9.5\pm 3.3$  years (2.5-14.3 years). The mean of clinical follow-up was  $13.0\pm 10.8$  months (range 1-30 months). EVL and/or Histoacryl injection was successfully performed in all children. Immediate control of bleeding was achieved in all cases. The number of rubber bands placed in all patients ranged from 2 to 6. Early slippage of the rubber bands were not been found in the post-EVL rebleeding. Varices relapse with rebleeding was observed in 4 of 15 (26.7%) patients after a mean time of  $14.8\pm 6.5$  weeks (5-24 weeks) follow-up. Patients with variceal rebleeding were retreated. Aggravated coagulation state, decreased platelets and ascites may be meaningful in predicting rebleeding. During follow-up, no fatal complication was observed in the patients. **Conclusion:** In children, the use of EVL and Histoacryl injection is safe and effective for the treatment of gastroesophageal varices. Effective measures for prevention and treatment of rebleeding should be adopted before and after operation.

### Key words

Children; Endoscopic variceal ligation; Esophageal varices; Gastric varices; Histoacryl injection

### Introduction

Acute gastroesophageal variceal bleeding is severe complication of portal hypertension in children and has high rates of morbidity and mortality. Gastric varices can occur

alone or in combination with esophageal varices and are often larger and located deeper in the submucosa than esophageal varices. Although the incidence of bleeding from gastric varices is relatively low (10%-36%), when it occurs it tends to be more severe, to require more transfusion, and to have a higher mortality rate than esophageal variceal bleeding.<sup>1,2</sup> Gastric varices have a high rate of rebleeding (38%-89%), and are classified as gastroesophageal varices (GOV-1) (esophageal varix extending down to the cardia or lesser curve) or GOV-2 (esophageal and fundal varices). Isolated gastric varices (IGV) may be located either in the fundus (IGV-1) or elsewhere in the stomach (IGV-2).<sup>3,4</sup>

With the advent of endoscopic therapy, the management of variceal bleeding has been greatly enhanced during the past decades. Endoscopic variceal band ligation (EVL) and Histoacryl injection are the most-used techniques to control or prevent variceal bleeding. Although EVL is well

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established as the treatment of choice for esophageal variceal haemorrhage, it is less effective for gastric varices.<sup>5-7</sup> Other endoscopic therapies for gastric variceal bleeding include injection therapy with standard sclerosants, Thombin or N-Butyl-Cyanoacrylate glue (Histoacryl). Endoscopic Histoacryl injection for gastric variceal bleeding was first reported in 1986 by Soehendra et al.<sup>8</sup> Histoacryl injection has been reported immediate haemostasis rate of 88%-100%.<sup>9-11</sup> Fuster et al reported good results from Histoacryl use in paediatric patients.<sup>12</sup>

In a population-based prospective study of major upper gastrointestinal bleeding, there was 1 annual incidence of portal hypertensive bleeding among 200,000 children.<sup>13</sup> Some retrospective studies in China found the incidence of esophageal varices was about 0.48%-0.75% in the children with digestive diseases.<sup>14,15</sup> 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. Few studies have examined the incidence of variceal bleeding among children with known varices diagnosed by endoscopy because few centers perform routine screening endoscopy.<sup>16</sup>

Variceal bleeding is difficult to treat because rebleeding risks. Furthermore, the endoscopic maneuverability in children is also more difficult than that in adults.<sup>17</sup> Until now, EVL and Histoacryl injection have not been developed widely and effectively in paediatrics comparing with adults. And there are very few studies have reported the possible predictive factors for rebleeding after EVL and Histoacryl injection in paediatrics. Therefore, the aim of present study is to investigate the efficacy, safety and feasibility of EVL and Histoacryl injection for the treatment of gastroesophageal variceal bleeding in children; and to assess the risk factors for variceal rebleeding after EVL and Histoacryl injection in paediatrics as a pilot study.

## Methods

### Patients

Fifteen children patients with esophageal varices and/or gastric varices were enrolled in this study between October 2009 and March 2012, underwent EVL and/or Histoacryl injection at our endoscopy center for treatment of variceal bleeding due to portal hypertension. There were 10 males and 5 females, and the average age was  $9.5 \pm 3.3$  years (2.5-14.3 years). Among these 15 patients, 5 cases were caused by congenital biliary atresia; 1 case was Caroli's disease; 1 case has inflammatory myofibroblastic tumour in liver;

cavernous transformation of the portal vein was the cause of 3 cases; 1 case was Budd-Chiari syndrome; and the remaining 4 cases were portal hypertension due to unknown pathogenesis.

Indications of ligation: acute esophageal varical bleeding; recurrence of esophageal varices after surgery; bleeding tendency in moderate and severe esophageal varices although having no history of bleeding (primary prevention); previous history of esophageal variceal bleeding (secondary prevention). Contraindications: upper gastrointestinal endoscopy contraindications; haemorrhagic shock uncorrected; hepatic encephalopathy  $\geq$ II period; too bulky or too small varicose veins.

Indications of tissue adhesive treatment: acute esophageal varical bleeding; red sign or surface erosion with history of bleeding in gastric varices (secondary prevention).<sup>18</sup>

All these patients complied with the indication. They all had active variceal bleeding, or had a high risk for bleeding varices and recent clinical history of anaemia. Four patients were repeatedly hospitalised because of recurrent bleeding. The clinical data, such as liver function, coagulation index, platelets, albumin, ascites, number of rubber bands placed, Histoacryl volume injected, and so on, were collected. These patients all had parental agreement to participate in the study after giving informed consent. Demographic data of our patients are summarised in Table 1.

**Table 1** Demographic features of the patients included in the study group

Sex (male/female) (%)	10/5 (66.7/33.3)
Mean age, year $\pm$ SD (range)	9.5 $\pm$ 3.3 (2.5-14.3)
Aetiology of portal hypertension(%)	
Biliary atresia	5 (33.3)
Caroli's disease	1 (6.7)
Inflammatory myofibroblastic tumour in liver	1 (6.7)
Cavernous transformation of the portal vein	3 (20.0)
Budd-Chiari syndrome	1 (6.7)
Due to unknown pathogenesis	4 (26.7)
Mean follow-up times (months)	13.0 $\pm$ 10.8 (1-30)
Mean Rebleeding times (weeks)	14.8 $\pm$ 6.5 (5-24)
GOV-1	0
GOV-2	12 (80.0)
IGV-1	0
IGV-2	0
PELD	18.6 $\pm$ 8.9 (7.0-30.0)

SD, standard deviation; GOV: gastroesophageal varices; IGV: isolated gastric varices; PELD: paediatric end stage liver disease

### Endoscopic Methods

Endoscopy was done with the patients under general anesthesia with intravenous propofol, tracheal intubation, and mechanical respiratory assistance. With use of a forward viewing endoscope (Olympus GIF XQ260, which has a diameter of 9.2 mm [Olympus Optical Ltd, Tokyo, Japan]; or Fujinon EG-410H2, which has a diameter of 9.3 mm [Fujinon Ltd, Tokyo, Japan]), the variceal injection was performed with a disposable macron-harbour varices injector (MHI-1, Wilson-Cook Medical, USA). The end of the endoscope was coated with silicone before the procedure. The injector was rinsed with saline solution, followed by lipiodol or 25% glucose liquid before and after Histoacryl injection (Beijing Suncon Medical Adhesive Co. Ltd, Beijing, China) ("sandwich method"). Rinsing with 25% glucose liquid was performed in the gastric cavity to avoid lipiodol embolism). 0.5-1.5 ml of the Histoacryl was injected in accordance to the number and extent of gastric varices on the bases of expert recommendations. Injector angle should be smaller than 30°, so that we could avoid injection was too deep to cause bleeding. The above procedures could be seen in Figure 1.

Saeed™ Multi-Band Ligator (MBL-6-F, Wilson-Cook Medical, USA) was used for EVL operation. Selected severe esophageal varices were visualised and aspirated into the banding chamber of the ligator. Suction was maintained until the screen became red, and then the band was deployed

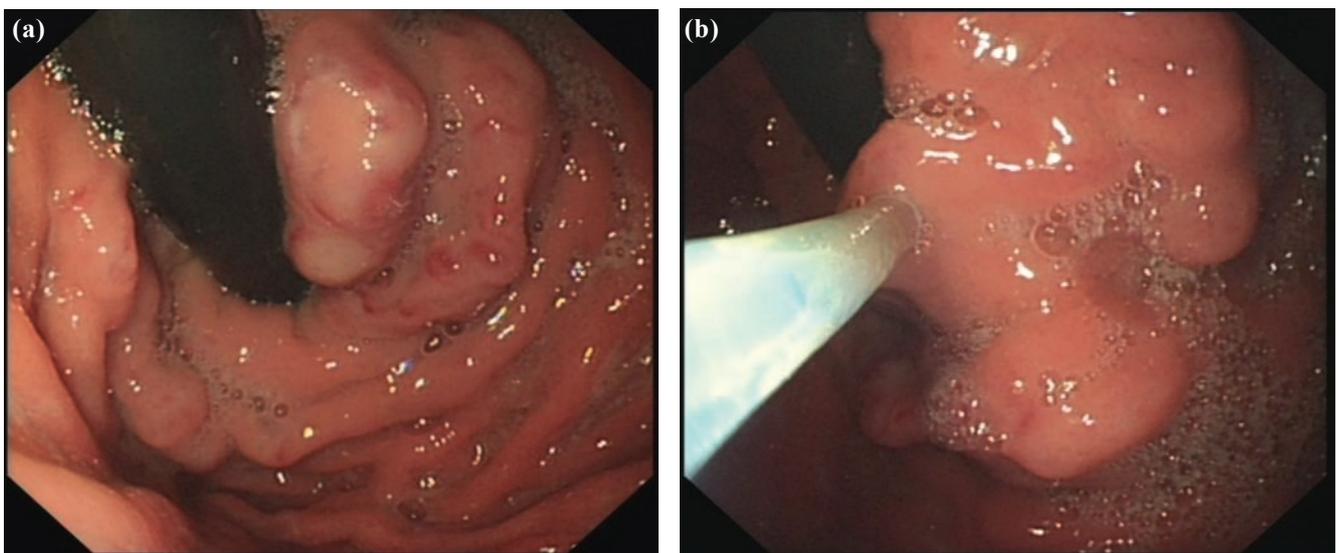
by rotating the handle clockwise until the band release was felt. The bands were then launched onto the selected varices in ascending order through the esophagus. The above procedures could be seen in Figure 2.

### Follow-up

Recommending a soft diet and avoiding strenuous exercise were applied. After each session, children were treated for 2 months or more days with an oral proton pump inhibitor (PPI) (omeprazole 1 mg/kg/d) until succeeding endoscopy. The day after the session, oral fluids were allowed in the 24h later. Unless there was acute bleeding, children were usually discharged 48 hours after the session. Early rebleeding is defined as: (1) recurrent haematemesis, and/or melena, and/or bloody fluid drained by nasogastric tube, occurs between 24 hours and 14 days after the operation; or (2) a decrease in haemoglobin by at least 20 g/L, or a transfusion of more than 2 units of concentrated RBC needed within 24 hours, or hypovolaemic shock occurs.<sup>19</sup>

### Statistical Analysis

Demographic, clinical, and endoscopic follow-up data were registered and analysed. Statistical analysis was carried out using SPSS 11.0. Mean and standard deviation were calculated and t-Test was used. The level of significance was adopted a P-values <0.05.



**Figure 1** Endoscopic Histoacryl® injection for treatment of gastric varices. (a) Endoscopic image showing a large gastric varix. (b) Injection of Histoacryl® into the gastric varix using the catheter.

## Results

All patients presented with haematemesis and melena and were confirmed having gastroesophageal varices by endoscopy. In this study, esophageal varices were not concurring with gastric varices always. Gastric varices and esophageal varices were both identified in 12 patients (80.0%). These 12 patients underwent EVL and Histoacryl injection varices at the same time. The rest 3 patients who presented esophageal varices underwent EVL only.

Among 12 patients who underwent EVL and Histoacryl injection: 1 case underwent three times of EVL and three times of Histoacryl injection; 2 cases underwent two times of EVL and one time of Histoacryl injection successively because of rebleeding. The rest 9 cases only underwent one time of EVL and Histoacryl injection at the same time. Haemostasis was typically achieved in all patients (100%). Early rebleeding was not occurred in 14 days. Varices relapse with rebleeding was observed in 4 cases of 15 (26.7%) patients after a mean of  $14.8 \pm 6.5$  weeks (5-24 weeks) follow-up. These 4 cases all had esophageal and gastric varices. Nevertheless, rebleeding happened in 4 of 12 cases (33.3%) who presented gastric varices and esophageal varices. 1 case has Caroli's disease; 1 case was Budd-Chiari syndrome; 1 case was caused by congenital biliary atresia; 1 case has inflammatory myofibroblastic tumour in liver. Repeated Histoacryl injection and esophageal variceal ligation were therefore necessary in 3 cases and the remaining 1 case died of hypovolaemic shock

after 3 months in the follow-up. Rebleeding did not happen in the 3 cases that who did not have gastric varices.

The volume of glue injected was  $0.86 \pm 0.32$  ml in non-rebleeding group and  $0.75 \pm 0.27$  ml in rebleeding group per variceal site. Immediate control of bleeding was achieved in all cases. The number of rubber bands placed in all patients ranged from 2 to 6. The more severe extent occurred in esophageal varices, the more rubber bands were ligated. Early slippage of the rubber bands were not been found in the post-EVL rebleeding in this study.

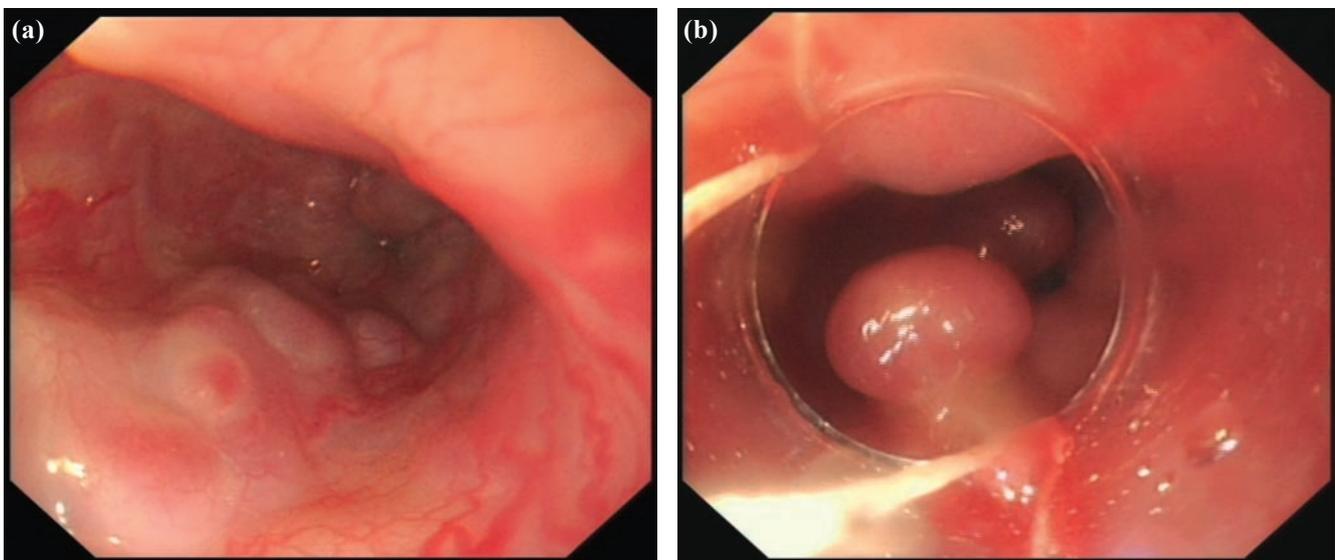
Liver function, platelets, ascites, number of rubber bands placed, prothromin time (PT)  $>18s$ , and so on, were taken account of for predicting the occurrence of rebleeding. Increased PT, decreased number of platelets may be more meaningful than the others for predicting occurrence of rebleeding ( $P < 0.05$ ). PT  $>18s$  and ascites perhaps may be also meaningful in predicting rebleeding than the others.

The mean of clinical follow-up was  $13.0 \pm 10.8$  months (1-30 months). In the operating process of injection and ligation, no active bleeding happened in any case. Infection and fatal complication were not been observed in all patients.

Clinical characteristics and endoscopic data were summarised in Table 2 and Table 3.

## Discussion

Variceal bleeding is an emergency with high rates of



**Figure 2** Endoscopic variceal band ligation for treatment of esophageal varices. (a) Endoscopic image showing a large esophageal varix. (b) Ligating the esophageal varix using Multi-Band Ligator.

mortality. In adults and children, the endoscopic therapy for variceal bleeding with EVL or Histoacryl injection is a well-established treatment that achieves 70% to 100% early haemostasis.<sup>20-22</sup> In both populations, significantly lower rates of complications and rebleeding are observed in EVL compared with sclerotherapy for the treatment of esophageal varices.<sup>20,22-23</sup> Good results were reported in Histoacryl use in paediatric patients for gastric varices.<sup>17</sup>

However, EVL technique in paediatric patients differs from that in adults in several ways because of (1) anatomical aspects with a small pharynx and esophageal lumen in children; (2) limited esophageal maneuverability, making this procedure sometimes very difficult.<sup>24,25</sup> EVL cannot be performed in all children because of the size of the child's esophagus compared to the scope size and the associated ligature attachment, which can significantly obscure the view from the scope. Because of the absence of an adapted banding device for smaller children, increased risk of iatrogenic trauma and perforation could be attempted in paediatric patients.<sup>26,27</sup>

Currently, portal hypertension in children most commonly results from an intrahepatic aetiology, cirrhosis, or sinusoidal obstruction, which can occur with a multitude of liver diseases but predominantly with biliary atresia. Studies from paediatric hepatology referral centers suggest that more than 50% of cirrhotic children have varices.<sup>28,29</sup> The most serious complication of portal hypertension is variceal bleeding. Variceal haemorrhage is associated with a significant mortality rate of up to 30%.<sup>30</sup> The natural history of variceal formation and bleeding in the presence of cirrhosis can occur fairly rapidly in children. 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.<sup>31</sup> A recent study of 139 children with biliary atresia found that 125 (90%) showed signs of portal hypertension and underwent endoscopy at a median age of 13 months. Of those 125 children, 88 (70%) had variceal formation. Gastrointestinal bleeding occurred in 20% of the 139 children at a median age of 17 months for the first bleeding, with 75% of them bleeding prior to 2.5 years.<sup>32</sup> In our study, the first variceal bleeding occurred in only 4 cases (26.7%) at a median age of 2.5 years, perhaps because the lack of attention from their parents.

EVL is subsequently developed and used in adults as an alternative treatment for esophageal varices, and is found to be superior to sclerotherapy.<sup>33</sup> Better results have been obtained with EVL, more than 77% primary

haemostasis and eradication rates, and lower rebleeding rates (<19%).<sup>34,35</sup> EVL could successfully arrest massive bleeding from ruptured esophageal varices, and Histoacryl injection could control the bleeding from gastric varices effectively. Another study investigated using EVL as a prophylactic measure to prevent first-time bleeding in children and adolescents with portal hypertension. Variceal ligation, however, is able to eradicate the varices in fewer sessions than the sclerotherapy group. Rebleeding rates prior to variceal eradication were higher in the sclerotherapy group than in the EVL group (25% vs 4%).<sup>26</sup>

In the process of our manipulation, no haemorrhage happened in any case. From our experience, EVL and Histoacryl injection were easily and safely to manipulate in older children. The youngest child was 2.5 years old. We need to apply the technique in more cases in future work. If we have suitable endoscopy with smaller diameter and macron-harbour varices injector for meticulous operation, we can apply the technique in much younger children.

Based on experience in our study, some aspects should be noticed in controlling varices bleeding and reducing complication. (1) coagulation function, platelets and ascites should be improved; (2) needle angle should be smaller than 30°, avoiding injection is too deep to cause bleeding; (3) the glue should be injected in vascular to eliminate varicose vein; (4) gastric varices should be treated with esophagus varices at the same time; (5) in order to avoid severe rebleeding, fully suction should be applied before launching bands, so that the bands would not release before varices was ischaemic necrosis; (6) appropriate haemostatic drugs and mucosal protective agents should be used after operation; (7) intraoperative and postoperative complications should be minimised, in order to achieve better haemostasis. In other studies, antibiotic prophylaxis was given in patients with cefazolin 25 mg/kg intravenously 30 minutes before the procedure.<sup>36</sup> We did not find infection occurring after the operation. Strictly sterile operating may be helpful to avoid secondly infection after procedure.

In our study, early rebleeding was not found. Four cases occurred rebleeding repeatedly and early slippage of the rubber bands were not been found in the post-EVL rebleeding, which were reported in adults studies. Precisely what triggers bleeding from varices is unknown. However, a number of risk factors for gastric variceal bleeding have been identified: location in the fundus, presence of red spots, and increasing size of the varices are the important factors in determining the risk of a first bleed from gastric

varices.<sup>37,38</sup> In our study, we did not find liver function, number of rubber bands placed or severity of varices had predictive meanings for varices rebleeding. Aggravated coagulation state, decreased number of platelets and ascites may be more meaningful in predicting the occurrence of rebleeding. The above result did not coincide with study in adults.<sup>39</sup> The coagulation index and ascites as independent predictive factors for rebleeding were reported in some previous studies,<sup>19,40</sup> as described in our study. In our study, gastric varices was more easily to happen rebleeding, this result was consistent with previous study.<sup>3</sup> The small number of samples may influence the data analysis. The

use of PPIs has been reported useful in comparison with a placebo, but the effect on preventing bleeding was not conclusive.<sup>41</sup> We still need large number of patients for further study. In addition, we did not observe fatal complications after the treatment, as previously reported in adult series.

Despite the limitations of this pilot study (small number of patients), we reported in all our cases immediate control of bleeding. It has been suggested that, after initial haemostasis with glue injection, secondary prophylaxis with EVL might be as effective as repeated injections in terms of rebleeding rate and long-term survival with fewer

**Table 2** Analysis for clinical characteristics

Variable	Non-rebleeding (n=11)	Rebleeding (n=4)
Male/Female	7/4	2/2
Age (year)	8.4±3.3	12.1±3.2
History of surgery		
Splenectomy	1 (9.1%)	0
Splenectomy and devascularisation	1 (9.1%)	1 (25.0%)
Splenectomy and devascularisation and splenorenal shunt	2 (18.2%)	0
Splenic artery embolisation	0	1 (25.0%)
Liver cancer surgery	1 (9.1%)	0
Ascites	1 (9.1%)	3 (75.0%)
Haematemesis and melena	11 (100%)	4 (100%)
Blood loss before EVL (mL)	11 (100%)	4 (100%)
Haemoglobin (g/L)	77.8±14.7	81.1±17.3
Haemoglobin <90 g/L	6 (54.5%)	2 (50%)
Platelets (10 <sup>9</sup> /L)	178.0±64.1	82.9±9.6*
Albumin (g/L)	36.3±7.5	32.9±5.5
Albumin <28 g/L	1 (9.1%)	1 (25%)
GPT (U/L)	28.8±18.2	17.0±8.5
PT (s)	15.0±1.3	19.5±1.4*
PT >18s	0 (0%)	3 (75.0%)
Mean follow-up (months)	9.1±7.2	12.9±9.8

EVL: endoscopic variceal band ligation; PT: prothromin time; GPT: glutamate pyruvate transaminase

\*P<0.05.

**Table 3** Analysis for endoscopic data

Variable	Non-rebleeding (n=11)	Rebleeding (n=4)
Esophageal varices grade		
Mild	0	0
Moderate	2	1
Severe	9	3
Extent of esophageal varies		
Middle and lower section	8	3
Whole	3	1
Red sign	9 (81.8%)	4 (100%)
Gastric varies	8 (72.7%)	4 (100%)
Number of rubber bands	4.1±0.9	3.2±0.8
Volume of Histoacryl injected (ml)	0.86±0.32	0.75±0.27

complications.<sup>42,43</sup> Recommending a soft diet and avoiding strenuous exercise is helpful in preventing early slippage. In conclusion, our study confirms the feasibility, efficacy, and safety of EVL and Histoacryl injection in the control of acute gastroesophageal variceal bleeding in children. Furthermore, aggravated coagulation state, decreased number of platelets and ascites may be meaningful in predicting the occurrence of rebleeding. Gastric varices should be treated with esophagus varices at the same time. Some aspects should be noticed in controlling varices bleeding and reducing complication.

Management of variceal bleeding in children focuses on preventing and controlling. Although the adult studies are important and are often the basis for empiric therapy in children, but these studies are not always suitable for paediatrics because of children's basic characteristics. Further studies are necessary to be carried out in paediatric patients.

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In our article, authors have no direct or indirect commercial financial incentive associated with publishing the manuscript. We state that the therapeutic substance have not any potential conflicts of interest for each of the authors. The authors would like to thank the team members of Professor Huang for their helpful discussion and critical reading of manuscript.

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