

## Retrospective Study

# Endoscopic cyanoacrylate injection for the treatment of gastric varices in children

Seak Hee Oh, Seung Jin Kim, Kang Won Rhee, Kyung Mo Kim

Seak Hee Oh, Seung Jin Kim, Kang Won Rhee, Kyung Mo Kim, Department of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul 138-736, South Korea

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**Correspondence to:** Kyung Mo Kim, MD, Department of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, 388-1 Pungnap-Dong, Songpa-Gu, Seoul 138-736, South Korea. [kmkim@amc.seoul.kr](mailto:kmkim@amc.seoul.kr)  
Telephone: +82-2-30103380

Fax: +82-2-4733725

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## Abstract

**AIM:** To evaluate the efficacy and safety of N-butyl-2-cyanoacrylate in treating acute bleeding of gastric varices in children.

**METHODS:** The retrospective study included 21 children with 47 episodes of active gastric variceal bleeding who were treated by endoscopic injection of N-butyl-2-cyanoacrylate at Asan Medical Center Children's Hospital between August 2004 and

December 2011. To reduce the risk of embolism, each injection consisted of 0.1-0.5 mL of 0.5 mL N-butyl-2-cyanoacrylate diluted with 0.5 or 0.8 mL Lipiodol. The primary outcome was incidence of hemostasis after variceal obliteration and the secondary outcome was complication of the procedure.

**RESULTS:** The 21 patients experienced 47 episodes of active gastric variceal bleeding, including rebleeding, for which they received a total of 52 cyanoacrylate injections. Following 42 bleeding episodes, hemostasis was achieved after one injection and following five bleeding episodes it was achieved after two injections. The mean volume of each single aliquot of cyanoacrylate injected was  $0.3 \pm 0.1$  mL (range: 0.1-0.5 mL). Injection achieved hemostasis in 45 of 47 (95.7%) episodes of acute gastric variceal bleeding. Eleven patients (52.4%) developed rebleeding events, with the mean duration of hemostasis being  $11.1 \pm 11.6$  mo (range: 1.0-39.2 mo). No treatment-related complications such as distal embolism were noted with the exception of abdominal pain in one patient (4.8%). Among four mortalities, one patient died of variceal rebleeding.

**CONCLUSION:** Endoscopic variceal obliteration using a small volume of aliquots with repeated cyanoacrylate injection was an effective and safe option for the treatment of gastric varices in children.

**Key words:** Cyanoacrylate; Gastric varix; Children; Endoscopic variceal obliteration; Complication

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**Core tip:** This is the first pediatric study using cyanoacrylate injection for acute gastric bleeding. The findings support its applicability to pediatric group.

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## INTRODUCTION

Endoscopic variceal ligation (EVL) has been shown to be effective and safe as first-line treatment of esophageal variceal bleeding in adults and children<sup>[1-3]</sup>. No method has become standardized, however, for the treatment of gastric variceal bleeding in children<sup>[1]</sup>. There have been no multicenter randomized controlled trials (RCTs), and only a few single-center RCTs, in adults<sup>[4-6]</sup>. The Baveno V consensus suggests endoscopic variceal obliteration (EVO) with N-butyl-2-cyanoacrylate (histoacryl) and EVL as first-line treatments for gastroesophageal varices (GOV) and for isolated gastric varices in adults<sup>[1]</sup>.

Although pediatric experts have also recommended EVO with N-butyl-2-cyanoacrylate for the management of bleeding from GOV in children, evidence for the management of gastric variceal bleeding in children is limited to case reports and uncontrolled case series<sup>[2]</sup>. In addition, the natural course and anatomy of gastric varices were only recently understood due to the development of interventional radiological procedures<sup>[7-9]</sup>. As mortality and rebleeding rates are higher for gastric than for esophageal varices<sup>[10-12]</sup>, endoscopic treatment guidelines must be established for gastric variceal bleeding in children. EVL is often not applicable to small children because their small pharynxes cannot adapt to conventional banding devices, resulting in esophageal injury from overtubes<sup>[13]</sup>.

Despite EVO with cyanoacrylate being more applicable to small children<sup>[14]</sup>, caution is needed prior to its use for gastric varices in children. Fatal complications, such as systemic embolism, have been observed in patients treated with cyanoacrylate for variceal bleeding<sup>[15,16]</sup>. This study evaluated the hemostatic effectiveness and safety of EVO with cyanoacrylate in the treatment of gastric variceal bleeding in children.

## MATERIALS AND METHODS

Between August 2004 and December 2011, 21 patients with gastric varices were managed using EVO with cyanoacrylate within 48 h after conservative management of gastric variceal bleeding at Asan Medical Center Children's Hospital. These 21 patients consisted of 8 boys and 13 girls, of median age 9 years (range: 9 mo-18 years). The mean height and weight of the children were  $120 \pm 26$  cm and  $21 \pm 14.4$  kg, respectively. Informed, written consent was obtained

from the parents of all the patients and the study was approved by our Internal Review Board.

Causes of portal hypertension included biliary atresia in nine patients (43%), extrahepatic portal vein obstruction (EHPVO) in five patients (24%), congenital hepatic fibrosis in two patients (10%), and Wilson's disease, autoimmune hepatitis, Budd-Chiari syndrome, hepatic vein occlusion, and liver cirrhosis due to cytomegalovirus hepatitis in one each of the remaining five patients.

Treatments prior to EVO included EVL in 10 patients (47.6%) and endoscopic injection sclerotherapy (EIS) with ethanolamine in two (9.5%). In particular, five of the younger and smaller patients (23.8%) failed the EVL due to difficulties in approach. The mean pediatric end-stage liver disease (PELD) score for the 16 patients younger than 12 years was  $3.9 \pm 12.8$  (range: -7-47), and the mean model for end-stage liver disease (MELD) score for the five patients who were 12 years or older was  $12.0 \pm 3.0$  (range: 9-17). Of the 21 patients, 16 (76.2%) were diagnosed with GOV type 1 (GOV1) and five with GOV2, with none having isolated gastric varices (IGV) according to the Sarin classification<sup>[17]</sup>. Varices were categorized according to their size as grade I-IV (I, < 3 mm; II, 4-6 mm; III, 7-10 mm; IV, > 10 mm). Most varices were of the largest size at the time of the first procedure, with 12 patients (57.1%) having grade III or IV varices. Morphological classification showed that 15 patients (71.4%) could be classified as having Form 2 (F2, tubular and beaded) and six (28.6%) as having Form 3 (F3, nodular) varices (Table 1)<sup>[18]</sup>. Esophageal varices of  $\geq$  grade II were noted among 16 (76.1%) children with GOV1 and GOV2.

Active gastric variceal bleeding (visible bleeding or clotted blood over a gastric varix) was confirmed within 24 h using diagnostic esophagogastrosocopy, in addition to the presence of large gastric varices and other sources of bleeding that are often present with hematemesis and melena. All patients received EVO as the secondary prophylaxis. Before active gastric bleeding developed, eight patients (38.1%) were taking  $\beta$ -blockers as primary prophylaxis.

### Treatment methods

EVO is not a well-established procedure, especially in children, so it was performed only in children who had developed gastric variceal bleeding. Efforts were focused on minimizing the risk of distant emboli, especially when treating small varices. The location and type of each gastric varix was endoscopically evaluated before the procedure, and the target varices were determined<sup>[8,9]</sup>. The injection catheter was inserted through the endoscope and the needle was inserted directly into each gastric varix. It was difficult to determine flow direction, even with GOV1, most of which drains into esophageal varices<sup>[8,9]</sup>. Although fluoroscopic examination and endoscopic

**Table 1** Baseline characteristics of the 21 patients treated with cyanoacrylate injection therapy *n* (%)

Clinical characteristics	<i>n</i> = 21
Male/female	8 (38.0)/13 (62.0)
Age (yr), median	8.7 (0.8-17.7)
Height (cm), mean	120 ± 26
Weight (kg), mean	21 ± 14.4
Etiology of the gastric varices	
Biliary atresia	9 (42.8)
Portal vein thrombosis	5 (23.7)
Congenital hepatic fibrosis	2 (9.5)
Budd-Chiari syndrome	1 (4.8)
Autoimmune hepatitis	1 (4.8)
Wilson's disease	1 (4.8)
Hepatic vein obstruction	1 (4.8)
Liver cirrhosis due to cytomegalovirus infection	1 (4.8)
mean PELD score (< 12 yr), mean	3.9 ± 12.8
mean MELD score (≥ 12 yr), mean	12.0 ± 3.0
Receiving $\beta$ -blocker medication	8 (38.1)
Sarin classification of the gastroesophageal varices	
GOV1	16 (76.2)
GOV2	5 (23.8)
Grade of the gastric varices	
Grade I	0 (0)
Grade II	9 (42.9)
Grade III	8 (38.1)
Grade IV	4 (19.0)
Form of the gastric varices	
F1	0 (0)
F2	15 (71.4)
F3	6 (28.6)

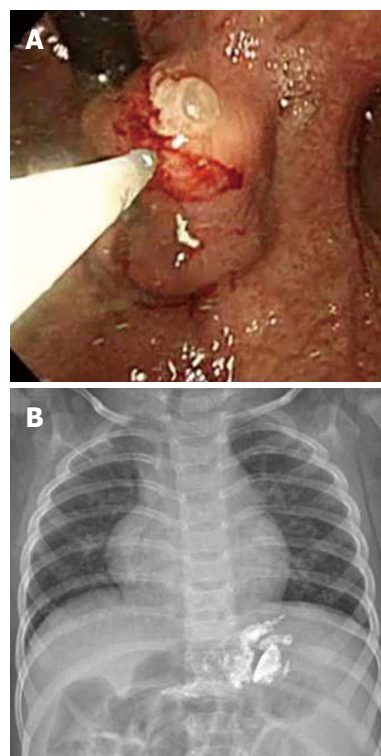
PELD: Pediatric end-stage liver disease; MELD: Model for end-stage liver disease.

ultrasonography could determine the size and location of collateral flow, neither was performed.

The EVO protocol in the present study was based on that used to treat adults<sup>[19]</sup>. Cyanoacrylate was repeatedly injected until the varices began to occlude, as determined by probing with a blunt probe. Cyanoacrylate injections were performed using the GIF series (Olympus Co., Tokyo, Japan) and disposable 23-gauge injection needle catheters (1.650 mm in length) (Figure 1). Each injection consisted of 0.1-0.5 mL of 0.5 mL N-butyl-2-cyanoacrylate mixed with 0.5 or 0.8 mL Lipiodol (cyanoacrylate:Lipiodol=1:1 or 1:1.6) (Guerbet, Aulnay-Sous-Bois, France). As small injection volumes are recommended when treating adults<sup>[19]</sup>, a small aliquot of a thick mixture of cyanoacrylate was preferentially used in treating children. It was also to minimize the number of injections and the amount of cyanoacrylate administered. The presence of distant emboli following treatment was reevaluated on chest and abdominal X-rays.

### Outcome measures

Successful hemostasis of active gastric variceal bleeding has been defined, according to the Baveno V criteria<sup>[1,2]</sup> as an absence of upper gastrointestinal bleeding for the first 120 h (5 d) after cyanoacrylate



**Figure 1** Endoscopic and radiographic images in one patient with extrahepatic portal vein obstruction. A: Intravascular injection of cyanoacrylate. The intravascular pressure was highest at the top of the variceal dome, leading to immediate extrusion of injected cyanoacrylate and massive uncontrollable bleeding. Thus, it was safer to first inject cyanoacrylate on the side of the varix; B: Chest X-ray after injection showing injected cyanoacrylate and Lipiodol without undesired embolism.

injection. Unsuccessful hemostasis was defined as death or the need to change the therapy due to (1) fresh hematemesis or naso-gastric aspiration that removed  $\geq 100$  mL of fresh blood  $\geq 2$  h after the procedure; (2) development of hypovolemic shock; or (3) a 3 g/L drop in hemoglobin within any 24 h period in the absence of transfusions<sup>[2,20]</sup>.

Rebleeding was defined as unsuccessful secondary prophylaxis, clinically significant rebleeding from portal hypertensive sources after day 5, or recurrent melena or hematemesis resulting in (1) hospital admission; (2) blood transfusion; (3) a 3 g/L drop in hemoglobin concentration; or (4) death within 6 wk. Treatment-related complications included (1) unplanned hospitalization or additional inpatient management; (2) death directly attributed to treatment; (3) treatment-associated infection such as pneumonia or peritonitis; (4) gastric perforation; and (5) distant embolization.

## RESULTS

### Hemostatic outcomes

The 21 patients experienced 47 episodes of active gastric variceal bleeding, including rebleeding, for which they received a total of 52 cyanoacrylate injections (mean number of sessions per episode  $1.1 \pm 0.3$ ). Following 42 bleeding episodes, hemostasis

**Table 2 Results in the 21 patients who received cyanoacrylate injections *n* (%)**

No. of sessions	Value
1	42 (89.3)
2	5 (10.7)
≥ 3	0 (0)
mean no. of sessions	1.1 ± 0.3
mean single aliquot of cyanoacrylate injection volume (mL) (range)	0.3 ± 0.1 (0.1-0.5)
Successful hemostasis	45 (95.7)/47 (95.7)
mean follow-up duration (mo)	30.2 ± 25.5
Number of rebleeding episodes	11 (52.4)/21 (52.4)
mean duration of hemostasis after EVO (mo)	11.1 ± 11.6
Number of patients with rebleeding within < 12 mo	5 (23.8)/21 (23.8)
Treatment-related complications	1 (4.8)/21 (4.8)

EVO: Endoscopic variceal obliteration.

was achieved after one injection and following five bleeding episodes it was achieved after two injections. The mean volume of each single aliquot of cyanoacrylate injected was  $0.3 \pm 0.1$  mL (range: 0.1-0.5 mL). Successful hemostasis was achieved after 45 of the 47 episodes (95.7%). In one of the two patients who failed to achieve bleeding control, EVO was interrupted due to hypotension caused by massive bleeding from a large fundal varix, whereas the second patient presented with a double aortic arch and tracheoesophageal narrowing, resulting in a failed endoscopic approach. The mean follow-up period was  $30.2 \pm 25.5$  mo (range: 0.1-101.0 mo). Eleven (52.4%) patients developed rebleeding events, and the mean duration of hemostasis after EVO was  $11.1 \pm 11.6$  mo (range: 1.0-39.2 mo). Five patients (23.8%) developed rebleeding episodes within one year. The success rate of secondary prophylaxis after primary EVO was 47.6% (Table 2).

### Complications and mortality

Treatment-related complications developed in only one patient (4.8%), whose hospitalization had to be extended because of abdominal pain and distension. Other complications, such as treatment-associated infection, gastric perforation, and distant emboli, did not occur. One patient was first suspected of having a pulmonary embolism, but it was later shown to be a pulmonary abscess and fistula between the distal esophagus and left lower lung that was complicated by previous esophageal variceal band ligation. During the follow-up, three patients received liver transplants, one underwent a Rex-shunt operation, and four died. Causes of death included variceal rebleeding in one patient, anaphylactic shock in one patient, and progression to hepatic failure in two patients.

## DISCUSSION

In general, EIS and EVL have been used to treat acute

bleeding from GOV in children<sup>[21,22]</sup>. However, the applicability of these treatment modalities for GOV in small children is limited due to insufficient evidence, technical difficulties, low success rates, and frequent complications<sup>[13,23-25]</sup>. For example, a banding device has not been developed for small children, whereas the overtubes of conventional devices may cause esophageal injury<sup>[13]</sup>. Moreover, the device tip often does not reach the bleeding loci of GOV due to the angled position of the fundus in children<sup>[23]</sup>. In addition, EIS is problematic in controlling acute GOV bleeding, especially from fundal varices (GOV2 and IGV1), with lower primary hemostasis rates<sup>[24]</sup>.

N-butyl-2-cyanoacrylate (histoacryl) is a tissue adhesive agent that rapidly hardens from a liquid form to a solid upon contact with hydroxyl ions in water<sup>[26]</sup>. Intravariceal injection of this compound, therefore, causes the varix to occlude rapidly upon contact with blood<sup>[23]</sup>. Although there have been only three case series on the use of N-butyl-2-cyanoacrylate for gastric varices in children<sup>[14,22,27]</sup>, studies in adults suggest that N-butyl-2-cyanoacrylate can be a promising alternative to EVL and EIS for controlling acute GOV bleeding. Recently, two large retrospective studies reported primary hemostasis rates of 95%-100% after cyanoacrylate injection for the control of acute GOV bleeding in adults<sup>[19,28]</sup>. In addition, a RCT found that the success rate of primary hemostasis in patients with acute GOV bleeding was higher with cyanoacrylate injection than with EIS (89% vs 62%)<sup>[6]</sup>, and two RCTs showed that the success rates of primary hemostasis for adults with acute GOV bleeding were similar or higher for cyanoacrylate injection than for EVL (87%-93% vs 45%-93%)<sup>[4,29]</sup>.

We found that the success rate of primary hemostasis in children was 95.7% in this study, similar to recent findings in adults. Cyanoacrylate was found to be effective in treating esophagogastric varices in children < 2 years old and < 10 kg; in that study, four children (19%) underwent EVO instead of EVL because of a device entry failure<sup>[14]</sup>. The overall rebleeding rate (52.4%) in this study was as high as the rate after EIS in adults (25%-70%)<sup>[30-32]</sup>. However, the rebleeding rate was 23.8% one year after the first injection of cyanoacrylate, similar to rebleeding rates of 22%-41% after 15-24 mo in adults<sup>[6,33,34]</sup>. Therefore, the efficacy of cyanoacrylate injection in primary hemostasis of acute GOV bleeding in children was high, although methods are needed to reduce the high rebleeding rate.

Several precautions must be taken during the endoscopic use of N-butyl-2-cyanoacrylate. Careful techniques are needed to prevent injury to the endoscopist's eye and to prevent blocking the biopsy channel of the endoscope. In addition, excessive dilution of cyanoacrylate carries a risk of fatal cerebral or pulmonary embolism. Small, relatively concentrated aliquots are therefore recommended for injection<sup>[19,35,36]</sup>. Most patients in this present study



were injected with a 1:1 mixture of cyanoacrylate and Lipiodol, and most were initially injected with 0.25-0.5 mL cyanoacrylate to prevent systemic embolisms. X-ray evaluation after the procedure showed the presence of Lipiodol in the upper esophagus along the esophageal varix, so small children were injected with a very small aliquot (0.2 mL) of a thick mixture of cyanoacrylate and Lipiodol. Distant emboli can be prevented by injecting small aliquots multiple times until variceal occlusion is achieved. No patient in the present study experienced distant emboli.

EVO-related complications and systemic embolic events, such as cerebral stroke, portal vein embolization, splenic infarction, and pulmonary embolism, have been reported in 4.6% of patients, along with bleeding ulcers in 2%-8% and sepsis in 1%-14%. These complications, however, are not usually life-threatening rates and are generally reversible. More frequently, mild complications, such as pyrexia (10%-35%) and chest or abdominal pain (5%-30%), have been reported<sup>[37]</sup>. Of our 21 patients, only one developed abdominal pain and distension, with no other patient experiencing complications. Hydrolyzation of cyanoacrylate results in the production of toxic substances, such as formaldehyde<sup>[38]</sup>, which has been shown carcinogenic in an animal model<sup>[39]</sup>. A similar tissue adhesive, 2-octyl cyanoacrylate, is available, showing similar efficacy and safety as N-butyl-2-cyanoacrylate in controlling GOV bleeding in adults<sup>[40]</sup>.

Portal hypertension in children is usually caused by biliary atresia and EHPVO and may have clinical consequences in the development of esophageal/gastric varices. Fortunately, the mortality rate (0%-8%) due to variceal bleeding is not as high in children as in adults<sup>[41]</sup>. Approximately 40% of children with biliary atresia develop variceal bleeding within 5 years, compared with 49% of patients < 16 years old and 76% of patients < 24 years old with EHPVO. Of 139 children with biliary atresia, 125 (90%) were diagnosed with portal hypertension; of the latter, 87 (70%) developed varices and 25 (20%) developed variceal bleeding<sup>[42]</sup>. In adults, the incidence of gastric varices (14%-36%) is lower than that of esophageal varices, but gastric varices result in more severe bleeding, a higher mortality rate (25%-55%), and a higher incidence of rebleeding (26%-89%)<sup>[10-12]</sup>. Currently, there are not enough pediatric studies on this issue.

In conclusion, this study suggests that endoscopic vascular obliteration using N-butyl-2-cyanoacrylate may be effective in children for the initial hemostasis of bleeding due to gastric varices, with a low rate of complications. This study was limited, however, by its inclusion of a small number of patients. The efficacy and safety of tissue adhesives, such as N-butyl-2-cyanoacrylate and 2-octyl-cyanoacrylate, for acute gastric variceal bleeding require validation in large, multicenter RCTs.

## COMMENTS

### Background

Gastric varix causes more severe bleeding and higher mortality than esophageal varix in children. However, few studies on treating acute gastric variceal bleeding are done in children.

### Research frontiers

This retrospective pediatric study is the first study to evaluate cyanoacrylate injection to treat acute gastric variceal bleeding in children.

### Innovations and breakthroughs

Repeated injections of a small volume of cyanoacrylate treated gastric variceal bleeding without embolism.

### Applications

Cyanoacrylate injection may be applicable to treatment of acute gastric variceal bleeding in children.

### Terminology

N-butyl-2-cyanoacrylate (histoacryl) is a tissue adhesive agent that rapidly hardens upon contact with water.

### Peer-review

This is a retrospective study of Cyanoacrylate injection for varices in the pediatric patients. The limitation was a small number of patients enrolled, however, interesting results.

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