ORIGINAL ARTICLE

Endoscopic treatment of gastroesophageal varices in young infants with cyanoacrylate glue: a pilot study

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Background: In children, endoscopic sclerotherapy and variceal ligation (EVL) are the most used techniques for the treatment of gastroesophageal variceal bleeding (VB). However, these techniques achieve poor results in cases of gastric variceal bleeding, and EVL is not applicable in young infants.

Objective: Our purpose was to evaluate the feasibility, efficacy, and safety of cyanoacrylate glue injection for the treatment of gastroesophageal varices in young infants.

Design: Single-center prospective study.

Patients: From 2001 to 2005, 8 young infants ($\leq$2 years old, $\leq$10 kg) with portal hypertension and gastroesophageal varices underwent treatment with *N*-butyl-2-cyanoacrylate.

Main Outcome Measurements: Demographic data and the results were registered and analyzed at 1, 6, and 12 months after treatment.

Results: The mean age and weight were 1.3 $\pm$ 0.42 years (range 0.8 to 1.9 years) and 8.5 $\pm$ 1.6 kg (range 5.5 to 10 kg). Glue injection was successfully performed in all infants. The mean volume injected was 1.15 $\pm$ 0.62 mL (range 0.5 to 2 mL). Immediate control of bleeding was achieved in all cases. Ulcer bleeding as a complication was observed in 1 case. Varices relapse with bleeding was observed in 3 of 8 (37.5%) patients after a mean of 12.5 $\pm$ 10.6 weeks (range 5 to 20 weeks). Patients with variceal rebleeding were retreated. Varices eradication was achieved in all cases after a mean of 1.4 $\pm$ 0.52 sessions (range 1 to 2 sessions).

Limitations: Open prospective series with a relatively small number of patients.

Conclusion: In young infants, the use of cyanoacrylate glue is safe and effective for the treatment of gastroesophageal VB. (Gastrointest Endosc 2009;■:■-■.)

Gastric varices (GV) are an infrequent but significant complication of portal hypertension in children. With the advent of endoscopic therapy, the management of variceal bleeding has been greatly enhanced during the past decades. Nevertheless, upper GI bleeding from GV is difficult to treat because of high morbidity and mortality rates and rebleeding risks. In pediatrics, as in adults, endoscopic variceal ligation (EVL) and endoscopic variceal sclerotherapy (EVS) are the most-used techniques to control or prevent variceal bleeding.[1] However, these techniques achieve poor results in bleeding from GV, and EVL is poorly applicable in young infants weighing less than 10 kg because of the absence of an adapted banding device. In adults, *N*-butyl-2-cyanoacrylate injection has been established as the more effective therapy for gastric variceal bleeding[2] and is also used for the treatment of large esophageal varices.

The aim of this pilot study was to investigate the feasibility, efficacy, and safety of *N*-butyl-2-cyanoacrylate for the treatment of gastroesophageal variceal bleeding in young infants.

Abbreviations: EVL, endoscopic variceal ligation; EVS, endoscopic variceal sclerotherapy; IGV, type II gastric varices; GOV, type 1 gastric varices; GV, gastric varices; PELD, pediatric end-stage liver disease; VB, variceal bleeding.

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METHODS

Study population

From May 2000 to April 2005, 8 young infants were prospectively selected to enter in this protocol. Young infants

were defined as small pediatric patients less than 2 years old and weighing less than 10 kg.

Inclusion criteria were (1) active gastric or gastroesophageal variceal bleeding, (2) patients with a high risk for bleeding varices and recent clinical history of anemia, and (3) parental agreement to participate in the study after giving informed consent. Exclusion criteria were (1) age >2 years, (2) weight >10 kg, and (3) participation in another clinical trial.

Active bleeding was defined as observed spurting or oozing of blood from varices or the presence of an overlying clot and a decrease in hemoglobin blood level less than 80 g/L.

Varices with high-risk characteristics were defined as fundal varices greater than 2 cm in diameter with the presence of stigmata of recent hemorrhage or red wale marks.[3-5]

All patients with active bleeding were received at the emergency endoscopy unit at the Edouard Herriot Hospital and underwent an intravariceal injection of *N*-butyl-2-cyanoacrylate within 24 hours of admission.

The severity of liver disease was classified according to the Pediatric End-stage Liver Disease (PELD) model.[6] PELD scores were calculated according to the following formula detailed in a previous report and then multiplied by 10 and rounded to the nearest integer:

$$\begin{aligned}\text{PELD risk score} = {} & 0.436\,age\,(<1\,\text{y}) \\ & - 0.687\,\log_e \text{albumin g/dL} \\ & + 0.480\,\log_e \text{total bilirubin mg/dL} \\ & + 1.857\,\log_e \text{international normalized ratio} \\ & + 0.667\,\text{growth failure}(< -2\,\text{SD}).\end{aligned}$$

GV were assessed by the classification of Sarin and Kumar[7] into 2 categories: (1) type I (GOV) GV (if communication between gastric and esophageal varices) and (2) type II (IGV), isolated fundal GV. Esophageal varices were graded in accordance to the classification of Paquet[8]: (1) small varices without luminal prolapse, (2) moderate-sized varices showing luminal prolapse with minimal obscuring of the gastroesophageal junction, (3) large varices (>2 cm in diameter) showing luminal prolapse substantially obscuring the gastroesophageal junction, and (4) very large varices completely obscuring the gastroesophageal junction.

Endoscopic method

Because of prior training in the use of glue injection, J. D. and T. P. were experienced in glue injection in adults and did the first cases in children together with A. L., until he considered that he had acquired sufficient autonomy.

Endoscopy was done with the patient under general anesthesia with intravenous propofol, tracheal intubation, and mechanical respiratory assistance. With use of a forward-viewing endoscope (Olympus GIF 160, which has a diameter of 8.6 mm [Olympus Optical Ltd, Tokyo, Japan]), the variceal injection was performed with a 19-gauge disposable sclerotherapy needle (ABS-Bolton Medical, Saint Michel sur Meurthe, France). The end of the endoscope was coated with silicone before the procedure. The injection needle was rinsed with saline solution, followed by Lipiodol Ultra Fluide (Guerbet, BP 57400, Roissy, France) before and after glue injection (rinsing with Lipiodol was performed in the gastric cavity to avoid Lipiodol embolism). *N*-butyl-2-cyanoacrylate plus methacryloxysulfolane (Glubran 2, GEM, Viareggio, Italy) was mixed with Lipiodol compound in a 1:1 ratio. Therefore, no more than 1 mL (by injection) of the solution was given in accordance with expert recommendations.[9] Antibiotic prophylaxis was given in all patients with cefazolin 25 mg/kg intravenously 30 minutes before the procedure.

After each session, children were treated for 10 days with an oral proton pump inhibitor (omeprazole 1 mg/kg/d). Chest radiography control was realized immediately after the injection. The day after the session, oral fluids were allowed in the morning and a fresh milk diet was allowed in the evening. Unless there was acute bleeding, children were usually discharged 48 hours after the session.

Endoscopic controls with clinical follow-up were performed at 1, 6, and 12 months after the index treatment. Variceal obliteration was assessed by blunt palpation with a catheter. If there was evidence of residual or rebleeding from GV, additional injections of Glubran 2 were given. Any clinical suspicion of GI bleeding was investigated by upper endoscopy.

Study assessment

Demographic, clinical, and endoscopic follow-up data were registered and analyzed. The feasibility, efficacy, and safety of the treatment were evaluated as follows: the feasibility was assessed by the technical aspect to perform the variceal injection, the efficacy was measured by the immediate control of bleeding and the variceal eradication at the follow-up, and the safety was assessed by the number of complications. Immediate control of bleeding was defined as the control of bleeding without rebleeding ≤ 72 hours after the treatment.

Capsule Summary

What is already known on this topic

- Endoscopic variceal ligation of bleeding gastric varices is poorly applicable in pediatric patients weighing less than 10 kg.

What this study adds to our knowledge

- In 8 children aged 2 years or younger weighing ≤ 10 kg who had gastroesophageal varices, treatment with *N*-butyl-2-cyanoacrylate glue resulted in immediate control of bleeding and variceal eradication in all cases after a mean of 1.4 sessions.

TABLE 1. Demographic features of the patients included in the study group

No. of cases (%)	8 (100)
Sex (male/female) (%)	2/6 (25/75)
Mean age, y ± SD (range)	1.3 ± 0.4 (0.8-1.9)
Mean weight, kg ± SD (range)	8.5 ± 1.6 kg (5.5-10)
Etiology of portal hypertension, no.	
Biliary atresia	4
Portal vein thrombosis	3
α_1-Antitrypsin deficiency	1
PELD score, mean ± SD (range)	20.1 ± 9.9 (8.0-36)
Follow-up, y ± SD (range)	0.5 ± 0.3 (0.2-0.9)

RESULTS

Six girls and 2 boys with a mean age 1.3 ± 0.4 years and a mean weight 8.5 ± 1.6 kg (range 5.5 to 10 kg) underwent *N*-butyl-2-cyanoacrylate treatment. The causes of portal hypertension were portal vein thrombosis (portal cavernoma) in 3 cases, biliary atresia in 4 cases, and α_1-antitrypsin deficiency in 1 case. Demographic data of our patients are summarized in Table 1.

The mean PELD score of the patients was 20.1 ± 9.9 (ranging from 8 to 36). Seven patients (87.5%) were referred because of upper GI bleeding, and one patient because of the presence of high-risk varices with recent history of anemia (three weeks ago). In 7 patients (87.5%), GOV were observed and in 1 case, IGV were found. All the patients also presented esophageal varices, being identified varices grade III in 4/8 cases (50%) and grade IV in 4/8 cases (50%). From the 7 patients with active bleeding, 4 patients presented oozing bleeding, 2 with spurting, and in 1 patient an underlying clot was found.

Injection of *N*-butyl-2-cyanoacrylate was successfully performed in all infants. The mean volume of glue injected was 1.15 ± 0.62 mL (range 0.5-2 ml). Immediate control of bleeding was achieved in all cases. Early complications included ulcer bleeding from the injected variceal site in 1 case 78 hours after cyanoacrylate injection. In this patient, the control of bleeding was obtained by using argon plasma coagulation (because we did observe ulcer oozing bleeding without persistent varices).

Varices relapse with rebleeding was observed in 3 of 8 (37.5%) patients after a mean of 12.5 ± 10.6 weeks (range 5-20 weeks). A second session of cyanoacrylate glue injection was therefore necessary. No fatal complication was observed in the patients. Complete eradication was achieved after a mean of 1.4 ± 0.52 sessions (range 1-2). The mean of clinical follow-up was 5 ± 3 months (range 2-8 months). During follow-up, 4 patients underwent liver transplantation. B-Blockers were not used as secondary prophylaxis in any of the children of the study group.

DISCUSSION

Variceal bleeding is an emergency with high rates of mortality. In adults and children, the endoscopic therapy for esophageal variceal bleeding with EVS or EVL is a well-established treatment modality that achieves 70% to 100% early hemostasis.[10-16] In both populations, significantly lower rates of complications and rebleeding are observed in EVL compared with EVS for the treatment of esophageal varices.[10,16-19]

GV are rare in children, with an increased incidence in patients treated previously by EVS from esophageal varices.[20,21] In pediatrics, EVL and EVS are generally used for acute bleeding by GOV.[21,22] However, as in adults, those therapies have demonstrated poor results. In fact, EVS shows low rates of primary hemostasis (66%) and eradication and a high rate of rebleeding in adult series, and it is therefore only recommended in acute GOV bleeding.[23] Better results have been obtained with EVL, more than 77% primary hemostasis and eradication rates, and lower rebleeding rates (< 19%).[23,24] However, this technique is limited to GV with a diameter no greater than that of the banding device.[25] On the other hand, the EVL technique in pediatric patients differs from that in adults in several ways because of (1) anatomic aspects with a small pharynx and esophageal lumen in infants and (2) limited esophageal maneuverability, making this procedure sometimes difficult.[15,16,20,26-28] In fact, the major problem with EVL is reflected in the smaller pediatric population (infants), on whom some authors discourage EVL because of the absence of an adapted banding device for these patients.[27] The minimal endoscope diameter for use with a banding device is 9.8 mm, with an increase at least of more than 12 mm with the ligator fitted. In small children, an increased risk of iatrogenic trauma and perforation could be attempted.[28]

N-butyl-2-cyanoacrylate plus methacryloxysulfolane (Glubran 2) is a polymerized adhesive substance that, in contact with blood, polymerizes a little more slowly than pure *N*-butyl-2-cyanoacrylate (Histoacryl).[9] It has been largely used in adults in prospective and randomized studies, showing better results compared with other techniques (EVS, EVL), especially to achieve gastric variceal bleeding control.[29,30] Reported complications include fever, necrosis of the GI wall, infections, rebleeding, perforation, needle varices sticking, and systemic embolism.[9] These complications have been explained and correlated to (1) the injection technique (instillation of large volumes of glue or the needle flushed distilled water per injection, the pressure of the glue injection) and (2) anatomic variants as spontaneous portosystemic shunts as a result of portal hypertension present in adult patients.[9,31,32]

The current study is the first to evaluate the feasibility, efficacy, and safety of using Glubran 2 in the treatment of gastric variceal bleeding in young infants. We defined our study population as children < 2 years of age and weighing < 10 kg; it was an arbitrary cutoff but was supported by our previous experience in young infants, in whom we were not able to use band ligation and were able to use sclerotherapy. Despite the limitations of this pilot study (small number of patients), we reported in all our cases immediate control of bleeding, with only 1 case of early ulcer bleeding as a complication of this technique. It has been suggested that, after initial hemostasis with glue injection, secondary prophylaxis with β-blockers might be as effective as repeated injections in terms of rebleeding rate and long-term survival with fewer complications.[33]

In addition, we did not observe fatal complications after the treatment, as previously reported in adult series. This could probably be attributed to our experience in adults with this technique in our center (since the early 1990s), the lesser total volume of glue used in our population, and the specific clinicomorphologic features of cirrhosis and portal hypertension in infants. Nevertheless, it must be well known that, although rare, cyanoacrylate injection may be associated with severe complications such as ulcers or even bronchoesophageal fistula, pulmonary embolism, and also paradoxic embolism, which may be due to the opening of the foramen ovale.[34,35]

In pediatrics, only 2 reports in older children have been described, and limited data are still available regarding *N*-butyl-2-cyanoacrylate in acute variceal bleeding. Fuster et al[36] describe 4 pediatric cases (mean age 9.6 years) of gastric variceal bleeding treated by cyanoacrylate. After a mean follow-up of 24.2 months, no rebleeding or fatal complications were observed. Itha and Yachha[21] also reported the use of Histoacryl in 7 children with bleeding by GOV (mean age 3.8 years), achieving good control of bleeding in 4 of 7 cases and without fatal complications. In spite of these encouraging results, it is difficult to establish recommendations, and prospective and randomized large studies are lacking, but probably difficult to do in spite of the small number of patients. However, we believe that this technique is a good alternative to standard pediatric endoscopic treatments or more invasive techniques used in infants, such as surgical devascularization with splenectomy, portosystemic shunts, and balloon-occluded retrograde transvenous obliteration.

In conclusion, our pilot study confirms the feasibility, efficacy, and safety of using *N*-butyl-2-cyanoacrylate in the control of acute gastroesophageal variceal bleeding in infants weighing less than 10 kg and aged less than 2 years. Further large studies are necessary to corroborate these results, including comparative trials with sclerotherapy.

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