

Endoscopic obliterative therapy with n-butyl-2-cyanoacrylate for gastrointestinal varices

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Abstract

Aims: To evaluate the utility of endoscopic obliterative therapy with n-butyl-2-cyanoacrylate (tissue adhesives) for gastrointestinal varices and to investigate the incidence of serious complications.

Methods: Endoscopic obliterative therapy with n-butyl-2-cyanoacrylate was performed on 228 gastrointestinal variceal patients; 221 gastric varices, 5 duodenal varices, and 2 anastomotic varices after choledochojejunostomy. Endoscopic therapy was performed under fluoroscopy using 70% or 83% cyanoacrylate diluted with 5% Lipiodol.

Results: Endoscopic obliterative therapy with cyanoacrylate for gastrointestinal varices was successful in all 228 cases. The incidence of serious complications was 4/228 (1.8%), including two cases of splenic infarction, one of pulmonary embolism, and one of an inflammatory tumor of the pancreatic tail, and all these 4 cases for gastric varices.

Conclusions: Endoscopic obliterative therapy with cyanoacrylate is a useful and relatively safe method for treatment of bleeding gastrointestinal varices. Nonetheless, careful attention must be paid to avoid potentially serious complications.

Introduction

Gastrointestinal variceal hemorrhage is a common complication with portal hypertension and is associated with higher morbidity and mortality rates than in patients with esophageal variceal bleeding. Gastric varices (GV) classified as gastroesophageal varices type 2 (GOV2) or isolated gastric varices 1 (IGV1) with Sarin classification [1] are more severe and often difficult to treat as compared to the other types of varices. Bleeding GV of these types can be treated successfully by injection of cyanoacrylate. N-butyl-2-cyanoacrylate (Histoacryl®, B.Braun Dexon GmbH Spangenberg, Germany) is a tissue glue monomer that polymerizes and solidifies instantly upon contact with blood. Soehendra et al. were the first to report the usefulness of n-butyl-2-cyanoacrylate in the treatment of bleeding GV [2].

On the other hand, ectopic varices are defined as portosystemic venous collaterals occurring anywhere in the gastrointestinal tract other than the esophagogastric region. Duodenal varices (DV) are considered ectopic varices, and account for 1-3% of all varices in patients with portal hypertension [3,4]. DV are reported to be the second most common cause of ectopic variceal bleeding after the rectal varices [5]. Bleeding from DV is generally massive, and diagnosis of ruptured duodenal varices along with the control of hemorrhage is difficult. Anastomotic varices after choledochojejunostomy are an uncommon cause of variceal bleeding, and it should be considered when evaluating gastrointestinal hemorrhage in patients with previous surgery and mesenteric venous hypertension.

Anastomotic varices after choledochojejunostomy drain directly into the intrahepatic portal vein. Therefore, endoscopic treatment is difficult for this condition and endoscopic obliterative therapy with

n-butyl-2-cyanoacrylate is the preferred treatment.

The aim of the present study was to evaluate the utility of endoscopic obliterative therapy with n-butyl-2-cyanoacrylate for gastrointestinal varices and to investigate the incidence of serious complications.

Methods

Patients

Two hundred twenty-eight patients with gastrointestinal varices and portal hypertension who underwent endoscopic obliteration therapy with n-butyl-2-cyanoacrylate were evaluated retrospectively (147 men and 81 women; age range, 30-81 years; mean, 62.5 years). Among these patients, 74 were emergency cases and the other 154 were prophylactic cases. The pathology underlying portal hypertension was liver cirrhosis (LC) in 206 patients, splenic vein occlusion (left-sided portal hypertension) in 9, extrahepatic portal obstruction in 8 (including 2 patients after choledochojejunostomy), and idiopathic portal hypertension in the remaining five. LC was confirmed by a combination of clinical, biochemical, and ultrasound criteria. Etiologies

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of cirrhosis in the 206 cases included 31 with hepatitis B surface antigen (HBs Ag) - positivity, 88 with hepatitis C virus (HCV) - positivity, 60 with alcoholic liver disease, 5 with primary biliary cirrhosis, one of autoimmune hepatitis, and 21 with unknown etiology.

The study was performed according to the Declaration of Helsinki, and was approved by the Ethics Committee at Sapporo Kosei Hospital. Written informed consent was obtained from all patients prior to the procedure.

Endoscopic findings

GV; according to the Sarin classification¹, IGV1 were present in 104 patients, GOV2 in 108, and ectopic varices seen outside the fundus (IGV2) in nine. DV; location of DV was the second portion of duodenum in 4 cases and duodenal bulb in 1. Anastomotic varices after choledochojejunostomy; endoscopy revealed large, coil-shaped varices in the afferent jejunal loop in 2 cases.

Methods

In 74 emergency cases, endoscopic examination was performed after stabilizing the general condition of the patients. When bleeding was spurting or oozing, a red or white plug, or tiny erosion, was observed at the gastrointestinal varices during emergency endoscopic examination (Figure 1), endoscopic obliteration using n-butyl-2-cyanoacrylate for hemostasis was performed immediately. Prophylactic endoscopic obliteration therapy using n-butyl-2-cyanoacrylate was performed on the remaining 154 patients due to the high risk of bleeding, which was determined by the presence of varices that enlarged in a short time, showed red color sign or erosion on their surface. Terlipressin was not routinely used before procedures.

For endoscopic oblitative therapy for gastrointestinal varices, we used n-butyl-2-cyanoacrylate diluted to a final concentration of 70% or 83% (except one case of duodenal varices) in 5% Lipiodol[®], (Guerbet Asia Pacific, Tsuen Wan, Hong Kong). Lipiodol[®] prevents the tissue adhesive from polymerizing too quickly and also allows for radiographic monitoring. Obliterative therapy was performed repeatedly every week with a 23-gauge needle until gastrointestinal varices disappeared. Fluoroscopic observation with an infusion of n-butyl-2-cyanoacrylate (avoiding flow into the systemic circulation) was performed to determine the extent of the varices (Figure 2a and 2b).

We evaluated the utility of endoscopic oblitative therapy with n-butyl-2-cyanoacrylate for gastrointestinal varices and assessed the incidence of serious complications.

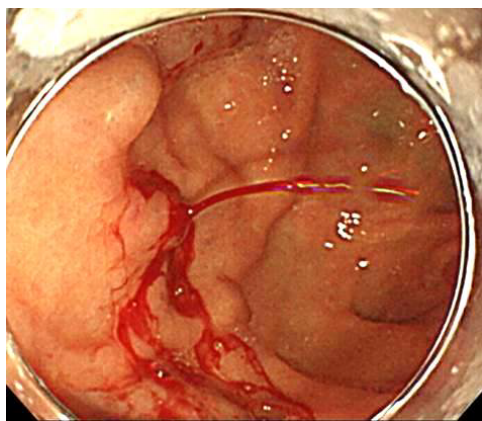


Figure 1. Spurting gastric variceal bleeding during emergency endoscopic examination.

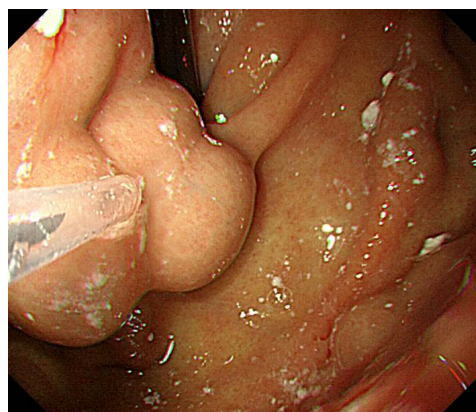


Figure 2a. Endoscopic oblitative therapy using 70% n-butyl-2-cyanoacrylate for gastric varices.



Figure 2b. Fluoroscopic image of endoscopic oblitative therapy.

Results

Endoscopic oblitative therapy with cyanoacrylate for gastrointestinal varices was successful in all 228 cases. The incidence of serious complications was 4/228 (1.8%), including two cases of splenic infarction, one case of pulmonary embolism, and one of an inflammatory tumor of the pancreatic tail, and all these 4 for GV.

1. Gastric varices (GV, n=221)

Eighteen of 68 emergency cases showed active bleeding from GV, whereas a fibrin plug or erosion of the variceal surface was detected in the other 50 patients. Endoscopic hemostasis was successful in all 68 cases. Among these 221 patients including prophylactic cases, the number of endoscopic treatments required for variceal eradication varied from 1 to 6. Total amount of n-butyl-2-cyanoacrylate used ranged from 1.5-8.0 ml with a mean of, 2.6 ml. For endoscopic oblitative therapy for GV, we used n-butyl-2-cyanoacrylate diluted to a final concentration of 70% in all cases. The incidence of serious complications was 4/221 (1.8%), including two cases of splenic infarction, one of pulmonary embolism, and one of an inflammatory tumor of the pancreatic tail. The two patients with splenic infarction improved under a conservative

medical treatment. The patient with pulmonary embolism showed no respiratory symptoms, and died of liver failure. The patient with the pancreatic tumor, which was diagnosed as an inflammatory tumor, was treated surgically.

2. Duodenal varices (DV, n=5)

Two of 4 emergency cases showed active bleeding from DV, whereas a fibrin plug or erosion of the variceal surface was detected in the other 2 patients. Endoscopic hemostasis was successful in all 4 in emergency cases. Among these 5 patients including prophylactic case, the number of endoscopic treatments required for variceal eradication varied from 1 to 2. Total amount of n-butyl-2-cyanoacrylate used ranged from 0.5-1.0 ml with a mean of, 0.7 ml. For endoscopic obliterative therapy for DV, we used n-butyl-2-cyanoacrylate diluted to a final concentration of 70% in 4 cases, and n-butyl-2-cyanoacrylate without contrast medium in 1 case of extrahepatic portal vein obstruction. The incidence of serious complications was 0/5 (0%) in DV. In 2 of 5 patients, balloon-occluded retrograde transvenous obliteration (B-RTO) was performed for remaining duodenal varices as an additional treatment.

3. Anastomotic varices after choledochojejunostomy (n=2)

One of 2 emergency cases showed active bleeding from anastomotic varices, whereas a fibrin plug or erosion of the variceal surface was detected in the other patient. Endoscopic hemostasis was successful in all 2. Among these patients, the number of endoscopic treatments required for variceal eradication varied from 1 to 2. Total amount of n-butyl-2-cyanoacrylate used ranged from 0.5-1.5 ml with a mean of, 1.0 ml. For endoscopic obliterative therapy for anastomotic varices, we used n-butyl-2-cyanoacrylate diluted to a final concentration of 83%. The incidence of serious complications was 0/2 (0%).

Discussion

N-butyl-2-cyanoacrylate polymerizes immediately on contact with blood, resulting in rapid hemostasis, and endoscopic treatment using this material is the first-choice endoscopic treatment worldwide for obliteration of bleeding GV [2, 6-11]. GV hemorrhage is associated with higher morbidity and mortality rates than those with esophageal variceal bleeding. Cardiofundal GV classified as GOV2 or IGV1 on the Sarin endoscopic classification¹ are more severe and often difficult to treat as compared to the other types of varices, and endoscopic obliterative therapy with cyanoacrylate is a good indication for these types of GV.

Currently, therapeutic strategies for GV bleeding include transjugular intrahepatic portosystemic shunt (TIPS) [12,13], cyanoacrylate endoscopic obliterative therapy and B-RTO, but the optimal management of bleeding GV remains controversial due to the lack of randomized, controlled trials. Large GV tend to bleed at lower pressures compared with esophageal varices [11], and TIPS seems to be less effective for treating GV bleeding than for esophageal variceal bleeding [14]. TIPS have been associated with problems in some patients, including complications such as encephalopathy and occlusion of the TIPS route [15,16]. Cost-effective analyses comparing cyanoacrylate injection therapy with TIPS have suggested that cyanoacrylate injection therapy is safe and effective for GV bleeding, in addition to being relatively lower in cost [17,18].

The B-RTO has been reported successfully for GV management, primarily in Japan [19]. As an elective use, however, it is unsuitable for acute GV bleeding. This procedure is very useful for the prevention of GV re-bleeding after endoscopic therapy. However, this procedure

induces an increase of portal pressure because of the obliteration of a large portosystemic shunt and results in significant aggravation of several associated problems, including ascites, hepatic hydrothorax, intestinal wall edema, and esophageal varices [20,21].

Endoscopic obliterative therapy with n-butyl-2-cyanoacrylate is useful for emergency control of acute gastric variceal bleeding of GOV2 or IGV1 types. Recent articles conclude that endoscopic obliterative therapy with n-butyl-2-cyanoacrylate is a highly effective modality for immediate hemostasis of gastric variceal bleeding and is associated with an acceptable re-bleeding rate [22]. Kumar et al reported that undiluted n-butyl-2-cyanoacrylate was effective in achieving initial hemostasis in case of actively bleeding gastric varices, and was very safe and not associated with embolic complications [22]. However, in many Japanese institutions, n-butyl-2-cyanoacrylate is mixed with a contrast medium, radiopaque Lipiodol[®], to allow radiologic monitoring during and after injection. To prevent n-butyl-2-cyanoacrylate from solidifying too quickly, dilution with Lipiodol is necessary.

Hemorrhage from DV is often a serious condition [3], with mortality as high as 40% at initial bleeding [23,24]. Varices in the duodenal bulb, which most frequently occur in the United States and Europe, are caused by extrahepatic portal obstruction (EHO). Several articles were reported about DV bleeding caused by EHO [25-27]. In Japan, duodenal varices are observed more commonly in the second portion of the duodenum [28]. Interventional radiologic techniques such as TIPS, B-RTO, are options for hemorrhaging duodenal varices and successful treatments have been reported, including TIPS [24] and B-RTO [29-31]. Endoscopic treatments have been performed successfully for duodenal varices. Endoscopic variceal ligation (EVL) is useful for obtaining hemostasis [28], however, re-bleeding of varices is a weak point with EVL. Additional treatment is recommended after EVL for duodenal varices. EIS has been performed successfully for the treatment of duodenal variceal bleeding [32], but there were serious problem of re-bleeding of the varices [24,33]. Endoscopic therapy using n-butyl-2-cyanoacrylate is also very useful for massive duodenal variceal bleeding [27, 34,35] because of the high blood velocity and blood flow. Hemorrhaging from varices in the jejunal loop, with extrahepatic portal vein obstruction after choledochojejunostomy, is a rare condition but several articles have been published [36-38]. Various medical treatments, such as interventional radiology and surgery, have been used to control bleeding from anastomotic varices after choledochojejunostomy; however, there is no best treatment strategy for anastomotic varices. [36,37,39,40] Endoscopic treatment is difficult for this condition and endoscopic obliterative therapy with n-butyl-2-cyanoacrylate is the preferred treatment for this type of varix [41,42].

Serious complications of n-butyl-2-cyanoacrylate, including embolization to the brain [43], portal vein [44], lung [45-50], and spleen [50,51] have also been reported. In this research, complications related to the procedure occurred in 4 patients, including 2 cases of splenic infarction, 1 case of pulmonary embolism, and 1 case of inflammatory tumor of the pancreatic tail, and all 4 cases were evaluated in the gastric variceal group. Risk factors for extravariceal embolization associated with n-butyl-2-cyanoacrylate treatment include a large injection volume, dilution of radiolucent n-butyl-2-cyanoacrylate with radiopaque Lipiodol[®], speed of injection, and the presence of shunts. The two main risk factors for extravariceal embolization with n-butyl-2-cyanoacrylate treatment include large injection volume, and dilution of radiolucent n-butyl-2-cyanoacrylate with radiopaque Lipiodol[®]. Larger volumes of n-butyl-2-cyanoacrylate used for treating varices of higher blood volumes increase the chance of leakage, and by

prolonging polymerization, overdilution with Lipiodol® can increase the risk of embolization. To avoid embolic complications as much as possible, we recommend that endoscopists aim to use the smallest volume of n-butyl-2-cyanoacrylate necessary for obliteration, and to use n-butyl-2-cyanoacrylate in the most concentrated form practicable.

Endoscopic oblitative therapy with a low concentration of n-butyl-2-cyanoacrylate has the potential to cause intrahepatic obstruction of the portal vein in the patients with anastomotic varices after choledochojejunostomy. Therefore, we carried out endoscopic oblitative therapy in these patients with a high concentration of n-butyl-2-cyanoacrylate.

Conclusion

In conclusions, our results demonstrated the high efficacy and relative safety of n-butyl-2-cyanoacrylate used in treating gastrointestinal varices. However, careful attention must be paid to avoid potentially serious complications.

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