

Endoscopic Obliterative Therapy with N-butyl-2-cyanoacrylate for Gastric Varices

Takahiro Sato*

Department of Gastroenterology, Sapporo Kosei General Hospital, Kita 3 Higashi 8, Chuo-ku, Sapporo 060-0033, Japan

Abstract

Aims: To evaluate the utility of endoscopic obliterative therapy with n-butyl-2-cyanoacrylate (a tissue adhesive) for gastric varices and to assess the incidence of serious complications.

Methods: Endoscopic obliterative therapy with n-butyl-2-cyanoacrylate was performed on two groups of patients with gastric varices. One group consisted of 129 patients from year 1992 through 2000, and the second of 92 from 2001 through 2014 (total=221). Endoscopic therapy was performed under fluoroscopy using 70% cyanoacrylate diluted with 5% Lipiodol.

Results: Endoscopic obliterative therapy with cyanoacrylate for gastric varices was successful in all 221 cases. The recurrence rate was 30/210 (14.3%) among patients where variceal eradication had been achieved. Additional treatment was successfully performed in all recurrent cases. The incidence of serious complications in the first group was 4/129 (3.1%), including two cases of splenic infarction, one of pulmonary embolism, and one of an inflammatory tumor of the pancreatic tail. In contrast, there were no serious complications was in the group treated later using smaller amounts of n-butyl-2-cyanoacrylate.

Conclusions: Endoscopic obliterative therapy with cyanoacrylate is a useful and relatively safe method for treatment of bleeding gastric varices.

Nonetheless, careful attention must be paid to the avoidance of potentially serious complications.

Keywords: N-butyl-2-cyanoacrylate; Endoscopic Obliterative Therapy; Gastric Varices; Histoacryl®

***Corresponding Author:** Takahiro Sato, Department of Gastroenterology, Sapporo Kosei General Hospital, Kita 3 Higashi 8, Chuo-ku, Sapporo 060-0033, Japan; Tel: +81 11 261 5331; Fax: +81 11 261 6040; E-mail: taka.sato@ja-hokkaidoukouseiren.or.jp

Introduction

Gastric variceal hemorrhage is a common complication of portal hypertension and is associated with higher morbidity and mortality rates than in patients with esophageal variceal bleeding. The Sarin classification of gastric varices divides them into Gastroesophageal Varices (GOV) or Isolated Gastric Varices (IGV) [1]. Cardiofundal gastric varices classified as Gastroesophageal Varices type 2 (GOV2) or Isolated Gastric Varices 1 (IGV1) are more severe and often difficult to treat as compared to the other types of varices.

Bleeding gastric varices 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 gastric varices [2]. Endoscopic obliterative therapy with n-butyl-2-cyanoacrylate is useful for treating bleeding gastric varices [3-7], but it has drawbacks that include embolic and septic complications. Our previous results demonstrated a high efficacy and relative safety of n-butyl-2-cyanoacrylate for treating gastric varices, but suggested that careful attention had to be paid to avoid potentially serious complications [8].

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

Methods**Patients**

Two hundred twenty-one patients with gastric varices and portal hypertension who underwent endoscopic obliterative therapy with n-butyl-2-cyanoacrylate were evaluated

retrospectively (143 men and 78 women; age range, 30-81 years; mean, 62.5 years). Among these patients, 68 were emergency cases and the other 153 were prophylactic cases; 85 patients were classified as Child-Pugh class A, 60 as class B, and 76 as class C. The pathology underlying portal hypertension was Liver Cirrhosis (LC) in 202 patients, splenic vein occlusion (left-sided portal hypertension) in 9 patients, extrahepatic portal obstruction in 5, and idiopathic portal hypertension in the remaining five. LC was confirmed by a combination of clinical, biochemical, and ultrasound criteria. Etiologies of cirrhosis in the 202 cases included 31 with hepatitis B surface antigen (HBs Ag) - positivity, 88 with Hepatitis C Virus (HCV) - positivity, 58 with alcoholic liver disease, 5 with primary biliary cirrhosis, one with autoimmune hepatitis, and 19 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

According to the Sarin classification [1], Isolated Gastric Varices (IGV1) were present in 104 patients, gastroesophageal varices into the greater curvature (GOV2) in 108, and ectopic varices seen outside the fundus (IGV2) in nine. The endoscopic findings were evaluated according to the general rules for recording endoscopic findings of esophago-gastric varices established by the Japanese Research Society on Portal Hypertension [9]. The variceal form was classified as small and straight (F₁), enlarged and tortuous (F₂), or large and coil-shaped (F₃). Variceal location was classified as cardiac (Lg-c, located adjacent to the cardiac orifice), fundal (Lg-f, located far from the cardiac orifice), or cardiac and fundal (Lg-cf, located between the cardiac orifice and the fornix), and gastric body varices (Lg-b, located in the gastric body due to left-sided portal hypertension). The Red Color (RC) sign reflects the presence of dilated small vessels or telangiectasia on the variceal surface. Among the 221 patients, 136 had F₂ type and 85 had F₃ type varices. Locations of varices were Lg-f in 107 patients, Lg-cf in 105, and Lg-b in the remaining 9 patients. Twenty of the 221 patients had RC-positive varices, whereas 43 showed erosion of the variceal surface. Twenty-five of the 211 patients were also afflicted by esophageal varices.

Methods

In the 68 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 gastric varices during emergency endoscopic examination (Figure 1 a, b), and endoscopic obliteration using n-butyl-2-cyanoacrylate for hemostasis was performed immediately. Prophylactic endoscopic obliterative therapy using n-butyl-2-cyanoacrylate was performed on the remaining 153 patients due to a high risk of bleeding, which was determined by the presence of varices that enlarged in a short time, showed the RC sign or erosion on their surface.

Figure 1-a: Spurting gastric variceal bleeding during emergency endoscopic examination.

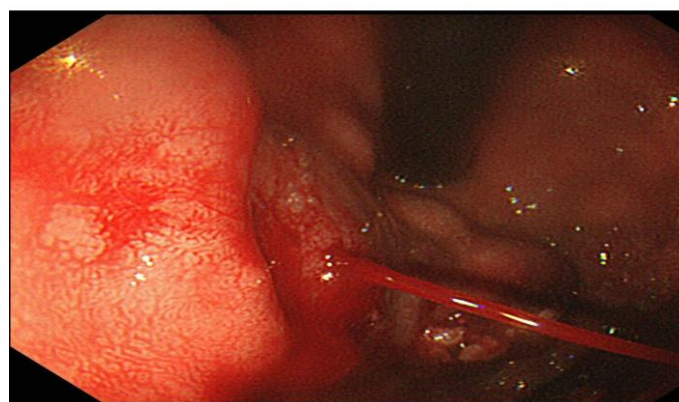
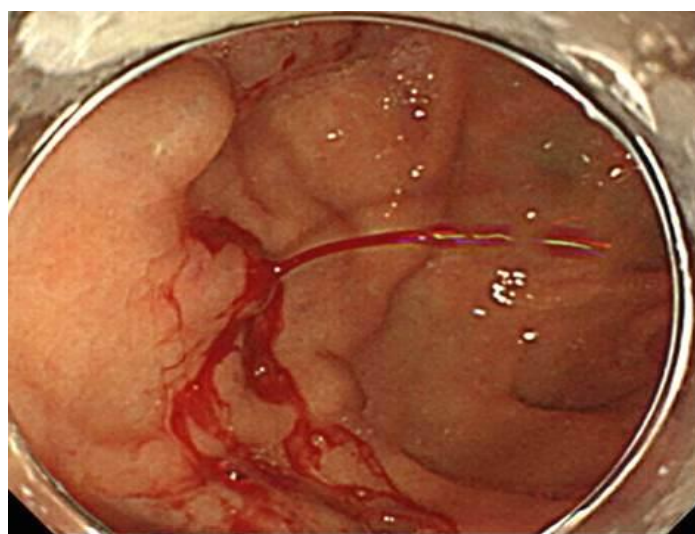


Figure 1-b: Endoscopic findings showing spurting gastric variceal bleeding.



For endoscopic obliterative therapy for gastric varices, we used n-butyl-2-cyanoacrylate diluted to a final concentration of 70% 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 with a 23-gauge needle until gastric varices disappeared. Fluoroscopic observation with an infusion of 70% n-butyl-2-cyanoacrylate (avoiding flow into the systemic circulation) was performed to determine the extent of the varices (Figure 2 a, b). Gastric variceal recurrence was defined by the RC sign on variceal surface or variceal bleeding.

Figure 2-a: Endoscopic obliterative therapy using 70% n-butyl-2-cyanoacrylate

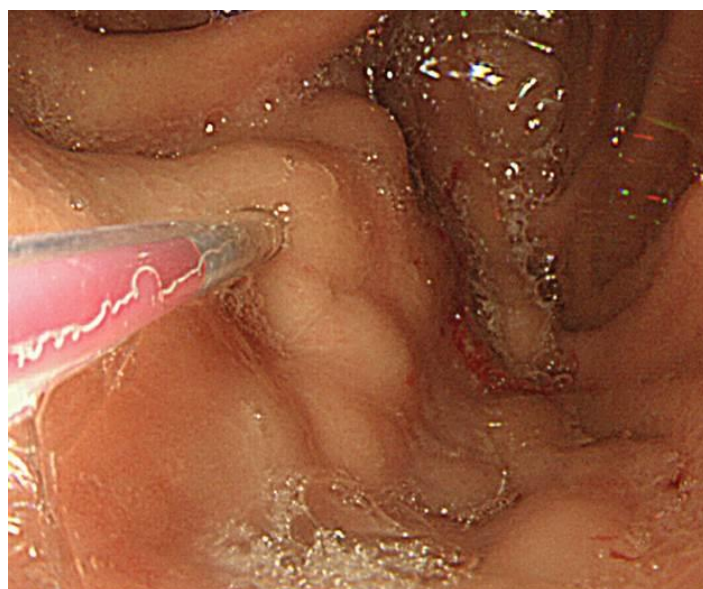


Figure 2b: Fluoroscopic image of endoscopic obliterative therapy



Endoscopic obliterative therapy with n-butyl-2-cyanoacrylate was performed on 221 gastric variceal patients (129 between 1992 and 2000; 92 from 2001 through 2014). To avoid embolic complications as much as possible, we used the smallest volume of n-butyl-2-cyanoacrylate necessary for obliteration in the latter group.

We evaluated the utility of endoscopic obliterative therapy with n-butyl-2-cyanoacrylate for gastric varices and investigated the incidence of serious complications in the two groups.

Results

Endoscopic obliterative therapy with cyanoacrylate for gastric varices was successful in all 221 cases. The recurrence rate was 30/210 (14.3%) among patients with variceal eradication. Additional treatment was successfully performed in all these recurrent cases.

In the first group, 10 of 45 emergency cases showed active bleeding from gastric varices, whereas a fibrin plug or erosion of the variceal surface was seen in the other 35 patients. Endoscopic hemostasis was successful for all 45 emergency cases. Eradication of gastric varices was achieved in 120 of 129 (93.0%) patients in total. Among these, the number of endoscopic treatments required for variceal eradication varied from 1 to 6. The total amount of n-butyl-2-cyanoacrylate used ranged from 1.5-8.0 ml with a mean of, 3.2 ml in these 129 cases. Gastric varices recurred in 17 of the 120 patients (14.2%) in whom eradication was achieved, but additional treatment was successful in all cases. The incidence of serious complications in the first group was 4/129 (3.1%), including two cases of splenic infarction (Figure 3), one case of pulmonary embolism, and one of an inflammatory tumor of the pancreatic tail. The two patients with splenic infarction improved under 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. The total amount of n-butyl-2-cyanoacrylate used in these four cases was 2.5-8.0 ml (mean 4.3 ml) as shown in Table 1.

Figure 3: Computed tomographic images depicting large infarctions encompassing 90% of the spleen after endoscopic obliterative therapy using n-butyl-2-cyanoacrylate (GV; gastric varices, SPA; splenic artery, SPV; splenic vein).

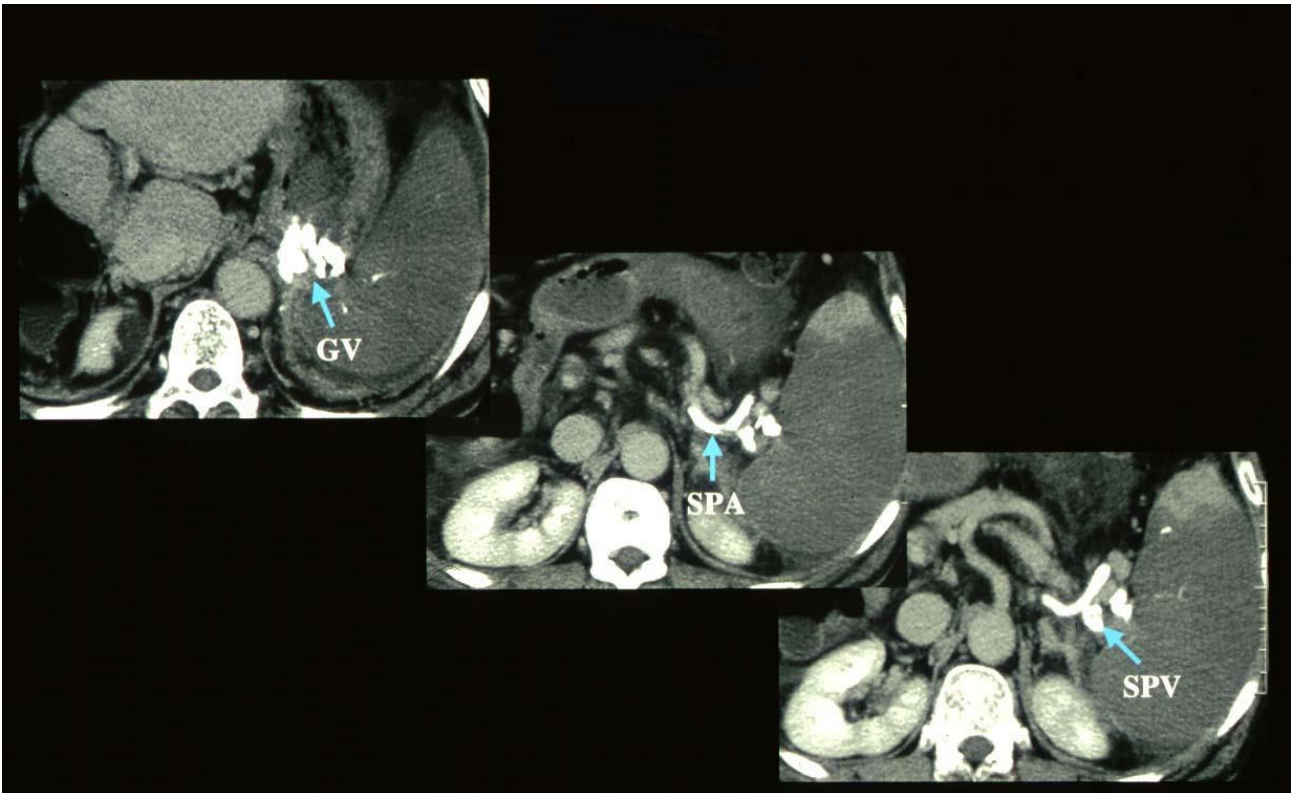


Table 1: Endoscopic obliterative therapy with cyanoacrylate

	Earlier group	Later group
Number of patients	129	92
Emergency cases	45	23
Total amount*	3.2 ml	1.9 ml
Recurrence rate	14.2%	11.1%
Serious complications	3.1%	0%

Earlier group: gastric variceal patients from 1992 through 2000

Later group: gastric variceal patients from 2001 through 2014

*Total amount of n-butyl-2-cyanoacrylate

In the later group, eight of 23 emergency cases showed active bleeding from gastric varices, whereas a fibrin plug or erosion of the variceal surface was seen in the other 15 patients. Endoscopic hemostasis was successful in all 23 emergency cases. Eradication of gastric varices was achieved in 90 of 92 (97.8%) patients. Among these patients, the number of endoscopic treatments required for variceal eradication varied

from 1 to 3. The total amount of n-butyl-2-cyanoacrylate used ranged from 1.0-3.0 ml; mean, 1.9 ml in these 92 cases. Gastric varices recurred in 10 of the 90 patients (11.1%) in whom eradication had been achieved, but additional treatment was again successful in all cases. There were no serious complications in the later group (Table 1).

Discussion

Gastric variceal hemorrhage is associated with higher morbidity and mortality rates than esophageal variceal bleeding. Cardiofundal gastric varices classified as Gastroesophageal Varices type 2 (GOV2) or Isolated Gastric Varices 1 (IGV1) according to Sarin [1] are more severe and often difficult to treat as compared to other types of varices. Currently, therapeutic strategies for gastric variceal bleeding include placement of a Transjugular Intrahepatic Portosystemic Shunt (TIPS), cyanoacrylate endoscopic obliterative therapy and balloon-occluded Retrograde Transvenous Obliteration (B-RTO). However, the optimal management of bleeding gastric varices remains controversial due to a lack of randomized, controlled trials. TIPS has been reported to be effective for the treatment of bleeding gastric varices [10, 11]. However, large gastric varices tend to bleed at lower pressures compared with esophageal varices [11], and TIPS seems to be less effective for treating gastric variceal bleeding than for esophageal variceal bleeding [12]. TIPS remains problematic in many patients, and is associated with complications such as encephalopathy and occlusion of the TIPS route, in addition to being relatively expensive, and sometimes proving ineffective [13, 14]. The B-RTO procedure involves inserting a catheter into the femoral vein and passage via the left renal vein and then to the outflow vein of the varices. Kanagawa et al., first introduced this procedure using ethanolamine oleate [15]. It has been reported that B-RTO is useful for the management of actively bleeding gastric varices and for the prevention of gastric variceal rebleeding after endoscopic therapy [16-19]. 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. N-butyl-2-cyanoacrylate polymerizes immediately on contact with blood, resulting in rapid hemostasis, and the use of this material is the first-choice for endoscopic treatment worldwide for obliteration of bleeding gastric varices [2-8]. Recent studies concluded 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 rebleeding rate [22, 23]. Kumar et al., reported that undiluted n-butyl-2-cyanoacrylate was effective in achieving initial hemostasis in cases of actively bleeding gastric varices, was very safe and was not associated with embolic complications [22]. However, in many 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. Serious complications, including embolization to the brain [24], portal vein [25], lung [26-31], and spleen [31, 32] have also been reported. In our study, complications related to the procedure occurred in 4 patients, including 2 cases of splenic infarction, one of pulmonary embolism, and one of an inflammatory tumor of the pancreatic tail. All 4 of these cases were evaluated in the first group, treated earlier. On the other hand, there were no serious complications in the later group with slightly modified procedure.

Two major risk factors for extravascular embolization associated with n-butyl-2-cyanoacrylate treatment were a large injection volume and, dilution of radiolucent n-butyl-2-cyanoacrylate with radiopaque Lipiodol®.

Additionally, the speed of injection and the presence of shunts also represented risk factor. Larger volumes of n-butyl-2-cyanoacrylate used for treating varices with 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 possible volume of n-butyl-2-cyanoacrylate necessary for obliteration, and to use n-butyl-2-cyanoacrylate in the most concentrated form practicable.

Conclusion

In conclusion, our results demonstrate the high efficacy and relative safety of n-butyl-2-cyanoacrylate used in treating gastric varices, but emphasize that careful attention is required to avoid potentially serious complications.

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