

• RAPID COMMUNICATION •

Bleeding gastric varices: Results of endoscopic injection with cyanoacrylate at King Chulalongkorn Memorial Hospital

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Abstract

AIM: To evaluate the efficacy and safety of gastric varices injection with cyanoacrylate in patients with gastric variceal bleeding.

METHODS: Twenty-four patients (15 males, 9 females) with gastric variceal bleeding underwent endoscopic treatment with cyanoacrylate injection. Successful hemostasis, rebleeding rate, and complications were retrospectively reviewed. Followed up endoscopy was performed and repeat cyanoacrylate injection was given until gastric varices were obliterated.

RESULTS: Seventeen patients achieved definite hemostasis. Of these, 14 patients had primary success after initial endoscopic therapy. Ten patients developed recurrent bleeding. Repeated cyanoacrylate injection stopped rebleeding in three patients. Transjugular intrahepatic portosystemic shunt (TIPS) was performed to control rebleeding in one patient which occurred after repeat endoscopic therapy. Six patients died (three from uncontrolled bleeding, two from sepsis, and one from mesenteric vein thrombosis). Minor complications occurred in 11 patients (six epigastric discomfort and five post injection ulcers). Cyanoacrylate embolism developed in two patients. One of these patients died from mesenteric vein thrombosis. The other had pulmonary embolism which resolved spontaneously. Advanced cirrhosis and hepatocellular carcinoma (HCC) were major risk factors for uncontrolled bleeding.

CONCLUSION: Endoscopic treatment for bleeding gastric varices with cyanoacrylate injection is effective for immediate hemostasis. Repeat cyanoacrylate injection has a lower success rate than the initial injection. Cyanoacrylate embolism is not a common serious complication.

INTRODUCTION

The source of variceal bleeding can be esophageal varices (EVs) or gastric varices (GVs). Generally, about 20% of patients with portal hypertension harbor GV, but only a few bleed from these^[1-3]. Unfortunately, bleeding GV is catastrophic and usually present with massive UGI bleeding. Many endoscopic techniques have been applied to control GV related bleeding. Rubber band ligation and sclerotherapy are the most preferred procedures for EVs treatment but neither of them seem to be effective enough to control GV related bleeding^[8-11]. Unlike EVs, GV related bleeding is very difficult to control by routine band ligation since retroflex position of the scope has to be used in order to reach GV. This in turn leads to difficult band deployment. Non-endoscopic methods, such as transjugular intrahepatic portosystemic shunt (TIPS) and surgical portosystemic shunts are effective but require experienced specialists^[4-7]. Moreover emergency shunt carries a high rate of post operative mortality^[6,7]. The discovery of tissue adhesive chemical has changed the management of gastric variceal bleeding. Cyanoacrylate (HistoacrylTM), a tissue adhesive, was first applied for endoscopic treatment of bleeding GV in 1980s. Thereafter, cyanoacrylate has become popular for this purpose in many countries. However, it is not available for use in the United States. We have retrospectively reviewed the safety and efficacy of endoscopic injection of cyanoacrylate for the treatment of UGI bleeding from GV at King Chulalongkorn Memorial Hospital.

Patients

There were 143 patients who presented with esophagogastric varices bleeding identified by endoscopy at King Chulalongkorn Memorial Hospital between January 2000 and 2003. Twenty-four patients (15 men and 9 women), mean age 48 years (29-75 years), had gastric variceal bleeding and all underwent endoscopic injection

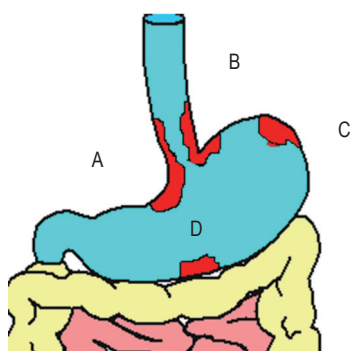


Figure 1 Classification of GV's on the basis of location and relationship with EV's (A and B: GOV, gastroesophageal varices, type 1 and 2 respectively. C and D: IGV, isolated GV's, type 1 and 2 respectively).

Table 1 Clinical characteristics of patients with bleeding gastric varices

	No. of patients	%
Total	24	100
Males:females	15:9	62:38
Mean age (Yr)	48	
Age range (Yr)	29-75	
Etiology of gastric varices		
- Cirrhosis	20	83.3
1. Viral hepatitis B	6	25.0
2. Viral hepatitis C	2	8.3
3. Alcoholism	9	37.5
4. Alcoholism and hepatitis B	2	8.3
5. Alcoholism and hepatitis C	1	4.2
- Primary biliary cirrhosis	1	4.2
- Idiopathic portal hypertension	3	12.5
Bleeding status		
- Active bleeding	9	38.0
- Recent bleeding	15	62.0
Child-Pugh classification		
A	6	25.0
B	11	45.8
C	7	29.2
Gastric varices classification		
GOV1	1	4.2
GOV2	17	70.8
IGV1	6	25.0
IGV2	0	0
Association with		
Hepatocellular carcinoma	6	25.0
Portal vein thrombosis	1	4.2
Hepatocellular carcinoma with portal vein thrombosis	1	4.2

of N-butyl-2-cyanoacrylate for hemostasis. Among these patients, nine had active bleeding (spurting or oozing) and the remaining 15 patients had evidence of recent variceal bleeding by demonstrating clot on gastric varices without any other potential source of bleeding.

Methods

Commercially flexible sclerotherapy injectors with a 6 mm/21-gauge needle were used for gastric variceal injection. N-butyl-2-cyanoacrylate (Histoacryl™, B. Braun, Melsungen, Germany), was mixed with Lipiodal™ (Laboratoire Guerbet, Aulnay-Sous-Bois, France) in 5:8 ratio and injected as a bolus dose of 2.6-5.2 cc, depending on the size of the GV's. Lipiodal was used to flush the needle before and after each injection. Generally injections

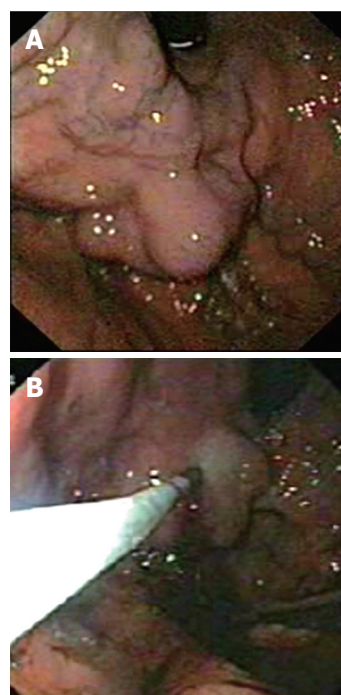
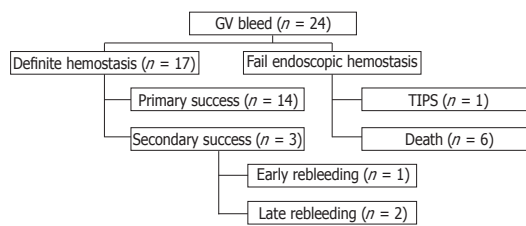


Figure 2 (A) (top) GV's at fundus, (B) (bottom) cyanoacrylate injection into the GV.

were directly delivered into gastric varices with active bleeding or containing stigmata of recent bleeding. Most procedures were performed by senior gastroenterologists under the supervision by experienced staff. At two week-follow-up endoscopy, reinjection was performed, if GV's were still detectable by palpation with the tip of biopsy forceps. An X-ray was taken after the injection to check the contour of the cyanoacrylate cast only in patients whom were suspected to have cyanoacrylate embolism. If there was recurrent bleeding during the follow-up period, reinjection with cyanoacrylate was also performed. Follow up endoscopy was performed in all the patients every two weeks and were followed up for a minimum of 4 wk. All patients who underwent endoscopic therapy received intravenous broad spectrum antibiotics prophylactically. Primary success was defined as an absence of recurrent bleeding after the first cyanoacrylate injection and during the follow-up period. Secondary success was defined as an absence of recurrent bleeding after reinjection of cyanoacrylate for recurrent bleeding. Definite hemostasis denotes primary or secondary success. A failure to achieve definite hemostasis was considered to be endoscopic failure. According to the classification proposed by Sarin *et al*^[2]. (Figure 1) gastric varices were classified by their location: varices in the esophagus and lesser curvature (GOV1); varices in the esophagus and gastric fundus (GOV2); varices in the fundus only (IGV1); or varices at other sites in the stomach or in the first part of the duodenum (IGV2). Status of cirrhosis was classified according to Child-Pugh classification^[12].

Statistical analysis

Data were expressed as percent, mean±SD, or median and range as appropriate. The prevalence of HCC and



Early rebleeding: rebleeding occurred within 24 h after endoscopic treatment.
Late rebleeding: rebleeding occurred after 24 h after endoscopic treatment.

Figure 3 Diagram demonstrating efficacy of cyanoacrylate glue for the treatment of GV bleeding.

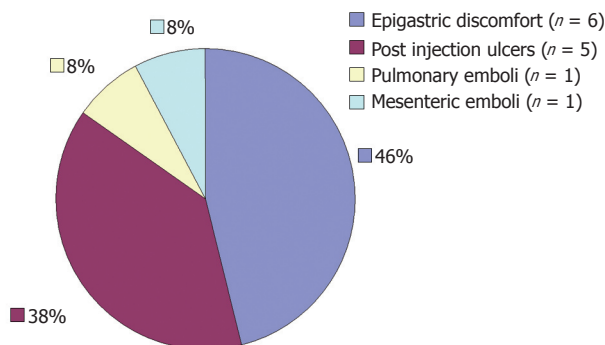


Figure 4 Complications of cyanoacrylate glue injection.

Child A, B or C cirrhosis in definite hemostasis group was compared to failed hemostasis group using Fisher's exact test. $P < 0.05$ was considered statistically significant.

RESULTS

All patients who had gastric varices bleeding underwent endoscopic injection of *N*-butyl-2-cyanoacrylate. Patients characteristics are shown in Table 1 (The mean duration of follow-up was 8.3 mo, range 1-34 mo). Figure 2 shows gastric varices in one of the patients. Intra gastric variceal cyanoacrylate injection was performed (Figure 2B) and the GV was disappeared at 4-wk follow up endoscopy. Seventeen patients (71%) achieved definite hemostasis. Primary success was achieved in 14 patients (58%) (Figure 3). The remaining three (12%) were classified as secondary success after repeat endoscopic injection of cyanoacrylate. The mean number of sessions to achieve definite treatment was 1.4. Seven patients (29%) failed to achieve definite hemostasis despite multiple sessions of endoscopic treatment (1 IGV 1, 2 GOV 2). In one patient, the bleeding was successfully controlled by TIPS procedure. The remaining six patients had conditions unsuitable for TIPS procedure. None of them were treated with sclerotherapy. Three patients died from refractory gastrointestinal hemorrhage with severe coagulopathy, two died from sepsis, and another died from cyanoacrylate induced mesenteric embolism and bowel infarction (Table 2). Six of the seven patients (85.7%) who failed to achieve definite hemostasis had higher prevalence of

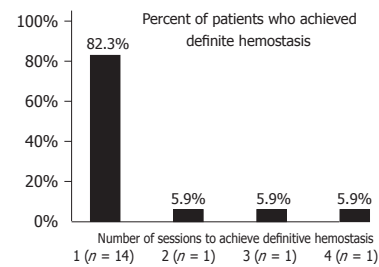


Figure 5 Number of sessions and percent of patients who achieved definite hemostasis ($n = 17$).

Table 2 Causes of death in patients who were unsuitable for TIPS

Causes of death	Number of patients
Uncontrolled GI bleeding	3
Sepsis	2
Mesenteric emboli and peritonitis	1

Table 3 Clinical comparisons of patients who achieved and failed definite hemostasis

	Definite hemostasis ($n = 17$)	Failed hemostasis ($n = 7$)
Hepatocellular carcinoma	1 (5.8%)	6 (85.7%) ¹
Cirrhosis Child A	5 (29.5%)	1 (14.2%)
Cirrhosis Child B	10 (58.8%)	1 (14.2%)
Cirrhosis Child C	2 (11.7%)	5 (71.6%) ²

¹Fisher's exact test, $P < 0.01$. ²Fisher's exact test of Child C *vs* non Child C between two groups, $P < 0.01$.

HCC compared to patients who had definite hemostasis ($P < 0.01$) (Table 3). Child C cirrhosis was presented more often in patients who failed definite hemostasis (71.6%) compared to patients who achieved hemostasis (11.7%, $P < 0.01$) (Table 3). Eighteen patients did not have serious adverse effects from cyanoacrylate injection. Six patients complained of epigastric discomfort which resolved spontaneously. Follow up endoscopy in five patients revealed asymptomatic post-injection ulcers at injection site from cyanoacrylate. Two patients developed serious complication from cyanoacrylate emboli. One patient died from small bowel infarction and peritonitis. This was found to be related to cyanoacrylate emboli since lipiodal stain was detected in the territory of mesenteric vein. The other patient developed chest pain and tachypnea 2 h after endoscopic treatment. Lipiodal stain was detected by a chest film. Fortunately, this patient survived after conservative treatment (Figure 4).

DISCUSSION

In asymptomatic portal hypertensive patients who underwent endoscopic surveillance for varices, GVs were detected less commonly than esophageal varices (EVs). The risk of GVs bleeding is also less but whenever bleeding occurs, it is dangerous and may be fatal^[2]. Unlike

EVs, endoscopic technique to control gastric variceal bleeding is very difficult due to the awkward position of the scope. All therapeutic devices have to come from retroflex position. In addition, blood in the fundus may obscure the view. Apart from endoscopic treatment, TIPS is the best alternative treatment for gastric variceal bleeding. Unfortunately, TIPS is not widely available. Endoscopic obliteration of bleeding gastric varices to achieve hemostasis has been reported from many centers around the world. Variety of sclerosing agents were used including alcohol, tissue thrombin, and cyanoacrylate. There have been reports that cyanoacrylate injection could control GV bleeding with excellent results^[13]. Generally, endoscopic variceal ligation (EVL) is one of the preferred treatments for EVs. Applying this technique for GVs is possible. However, there is a significant limitation due to the position of the scope and size of GVs. Gastric varix that is larger than 2 cm in diameter may be difficult to suck in to the tip of the scope while performing EVL. Therefore, incomplete endoscopic ligation may occur. The residual varix with high pressure may be prone to recurrent bleeding. A recent study reported by Lo *et al*^[14], concluded that endoscopic obliteration using band ligation is less effective and more difficult than cyanoacrylate injection in the management of bleeding gastric varices. Endoscopic variceal injection by other agents beside cyanoacrylate such as alcohol appeared to be less effective. This has been confirmed by Sarin *et al*^[15], who showed that cyanoacrylate injection was significantly more effective in achieving variceal obliteration than alcohol injection. Furthermore, complete obliteration was achieved within a few weeks by injection of a smaller volume of the agent. In addition they also found that cyanoacrylate injection was able to stop acute GV bleeding more often than alcohol injection and the need for rescue surgery was less.

Our study has shown that bleeding GVs was controlled by the first session of cyanoacrylate injection in 14 of 17 patients (82.3%) who achieved definite hemostasis (Figure 5). Second injection was less effective resulting in definite hemostasis in only 30% of patients (3/10) who failed initial injection. The mean number of session for endoscopic therapy to achieve hemostasis in our series was lesser than a series from UK ($1.4 \text{ vs } 2 \pm 1$)^[16]. In our series, large volume of cyanoacrylate injection was used during the initial treatment and majority of GVs were obliterated. This in turn may lead to a less number of endoscopic sessions. The overall success rate is usually determined by definite hemostasis. Our success on definite hemostasis is lower than the previous study by Lo *et al*^[14], (71% *vs* 87%).

We found that patients who failed definite hemostasis had more advanced stage of liver disease than patients who achieved definite hemostasis. In addition, HCC was found more often in failure group (6 of 7 patients) compared to success group (1 of 17 patients) (Table 3). Endoscopic related complications from cyanoacrylate injection are generally minor and spontaneously resolved such as epigastric discomfort, nausea, vomiting, and ulcer at the injected site.

However, fatal complication may occur. The most

dangerous complication is glue embolism. There have been many reports regarding this type of complication. For example, there was a case report of cerebral embolism after glue injection. Glue was found in the left atrium by echocardiography. Cardiac surgery was performed and intracardiac glue was removed^[17]. A retrospective study from UK reported pulmonary embolism after glue injection in 1 of 23 cases^[16]. Another larger study from Taiwan reported no case of pulmonary embolism after glue injection in 90 patients with bleeding gastric varices^[18]. Unfortunately, one of the patients in our series developed generalized peritonitis, 8 h after glue injection. The lipiodal stain was detected from abdominal X-ray. This patient expired 2 d later without undergoing laparotomy due to his poor condition. During the period of our study, all patients received prophylactic antibiotics. Despite this protocol, there were two patients who died from septicemia. Sarin *et al*^[15], reported that 9 of 17 patients developed fever following glue injection for GVs. A case report from Malaysia showed that a patient developed multiple systemic emboli with septicemia after elective glue injection for fundic varices^[19]. Fortunately, the patient recovered completely after intensified supportive treatment. Prophylactic administration is becoming a standard protocol for cirrhotic patient with active upper gastrointestinal hemorrhage^[20]. However, antibiotic prophylaxis for elective glue injection is still controversial. Our recent unpublished data did not discover any bacteremia in the patient who underwent elective glue injection for GVs.

In conclusion, the results of the present study demonstrated that endoscopic injection of cyanoacrylate is effective to control majority of GVs related bleeding within the first session of treatment. Repeat endoscopic treatment is less effective than the initial injection. Advanced staged cirrhosis and HCC are major risk factors for failed hemostasis after cyanoacrylate injection of GVs.

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