

# COMPLICATIONS OF NECROSIS ULCER ON ENDOSCOPIC TISSUE ADHESIVE INJECTION IN VARICEAL BLEEDING

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## ABSTRACT

Endoscopic variceal obturation with tissue adhesive injection is a mainstay treatment to control gastric variceal bleeding. We looked into the side effects and risks that come with this treatment in a subject. Therefore, this study aimed to evaluate and present a case study of this type of complication. A retrospective complications analysis was performed of a 57-year-old male patient with gastric variceal hemorrhages who was admitted to tertiary care. The patient received N-butyl-2-cyanoacrylate as therapy for endoscopic variceal obturation. Four days past the surgery, the patient experienced recurrent and uncontrolled massive hematemesis and later died of uncontrollable bleeding. This report concludes that although complications from endoscopic variceal obturation with Histoacryl glue N-butyl-2-cyanoacrylate in the treatment of gastric varices are uncommon, they may still occur.

**Keywords:** Variceal Bleeding, Endoscopy, Tissue Glue Complication, Necrosis, Histoacryl

## 1. INTRODUCTION

Acute variceal bleeding refers to varicose veins and in the absence of other identifiable causes. Gastric variceal bleeding is one of the serious complications of liver cirrhosis and is the second most common cause of death in patients with liver cirrhosis. Varicose veins due to pulmonary hypertension associated with cirrhosis form in 30-60% of patients as a physiological compensation for lowering portal venous pressure with the majority of patients developing cirrhosis with one-third developing acute variceal bleeding [1,2].

The prevalence of gastroesophageal varices varies but can reach 80% in patients with decompensated cirrhosis; this statistic goes up by 7% each year. Variceal bleeding is highly dependent on the size of the varicose veins with prognostication strongly related to the severity of the liver disease. Bleeding-related mortality in the first 6 weeks is up to 30% in cases of advanced liver disease (Child C) with rebleeding rates reaching 60% [3].

The mainstay of treatment for acute variceal bleeding in a well-equipped center involves fluid resuscitation, prophylactic antibiotics, and administration of a vasoactive agent, e.g., terlipressin, combined with endoscopic intervention. Cyanoacrylate glue injection via an endoscopic approach is one of the most commonly used methods to control acute variceal bleeding. Although the complications of this method are very low, there is still the possibility of complications related to the procedure, such as mucosal necrosis, ulceration, and bleeding [1,2].

This report will discuss the cases of necrotizing ulcer complications in patients with gastric varices associated with hepatic cirrhosis in patients with chronic hepatitis B after undergoing endoscopic injection of Histoacryl glue in acute variceal bleeding.

## 2. CASE PRESENTATION

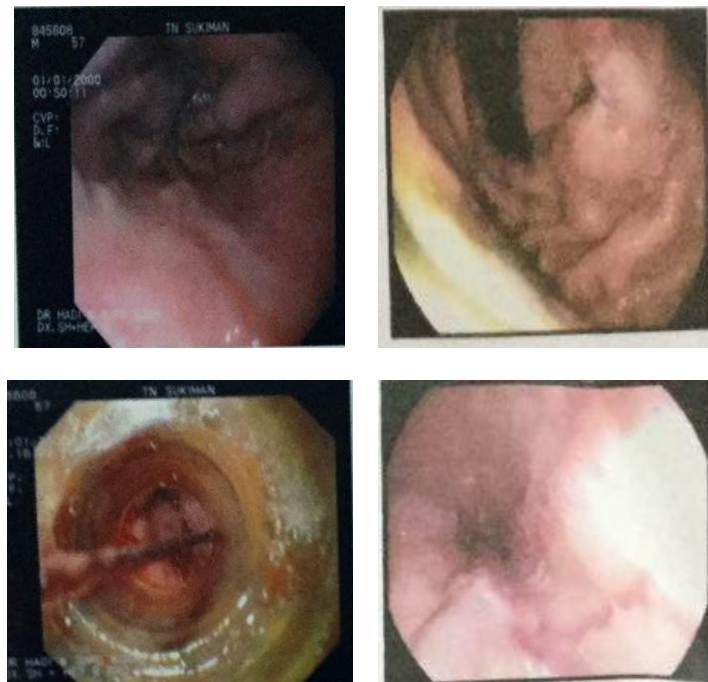
ST, a 57-year-old male private-sector worker, was referred by a private hospital. Since a day before admitting himself to the hospital, ST complains of the following: 1) dark blood vomit and soft blob stool; 2) recurrent pain in the pit of the stomach; 3) nausea when eating. Each time ST vomits or passes stool, he reported feeling weak. The patient denied any fever, loss of consciousness, shortness of breath, or chest pain.

The previous month, ST had undergone an ultrasound examination of the abdomen and viral hepatitis on the basis of black stool and bright red blood vomit. An abdominal ultrasound (US) found cirrhosis of the liver, with reactive hepatitis B, non-reactive anti-HCV, and quantitative HBV DNA detected  $5.96 \times 10^2$  IU/ml ( $34,68 \times 10^2$  copies/ml). Endoscopy results found grade II-III esophageal varices in the distal 2/3 of the esophagus and varices in the gastric fundus. Subsequently, sclerotherapy was performed.

When prompted, the patient denied any history of diabetes, hypertension, liver disease, or jaundice. From a physical examination, the male patient has a generally weak condition, compos mentis, a height of 160 cm and a weight of 54 kg, blood pressure of 110/60 mmHg, a pulse of 68 times per minute, breathing 20 times per minute, and axillary temperature 37.1° C. The conjunctiva was slightly anemic and the sclerae were slightly icteric. There were no enlarged cervical lymph nodes found in the patient. There was no increase in jugular venous pressure. Chest examination discovered symmetrical chest movements, no retractions, a single S1–S2 heart sound with no extra heart sounds. Breath sounds were vesicular in both lung fields, no crackles or wheezes were found. The abdominal wall had soft tissues and minimal ascites. There was no enlargement of the liver and spleen. As for the extremities, there was minimal edema in both limbs with warm acral.

The patient's blood examination results are as follow: Hb 6.6 g/dL, HCT 26.6%, Leukocytes  $5.730/\text{mm}^3$ , granulocytes 81.8%, platelets  $192,000/\text{mm}^3$ , SGOT 194, SGPT 51, serum albumin 2.66, total bilirubin 2.59, direct bilirubin 1.99, sodium 136, potassium 4.0, Chloride 108, BUN 25, Serum creatinine 0.78, PPT 13.5 (control 11.7), APTT 26.3 (Control 24.4). The ECG showed a sinus rhythm (SR) at a rate of 68 beats per minute, with normal frontal and horizontal axes. Chest X-ray showed no abnormalities. The patient's endoscopy found grade II-III esophageal varices, with ulcers in the LEGV according to the Forrest I b classification (Figure 1).

Based on the examination results, the patient was diagnosed with hematemesis with melena due to gastric necrotic ulcer (Forrest I b) at the oesophageal junction, normochromic normocytic anemia, hypoalbumin, and hepatitis B-related liver cirrhosis. The patient was given a liquid diet of hepatosol via NGT 6x100 cc, transfusion of PRC 1 bag/day up to Hb  $\geq$  9 g/dl, 500 cc of aminofusin liver infusion for every 24 hours, omeprazole pump of 8 mg/hour for 72 hours, 15 cc of sucralfate orally every 8 hours, 20 mg of propranolol for every 8 hours, 600 mg of telbivudine for every 24 hours and planned for esophagogastroduodenoscopy (EGD) re-evaluation in one week.



**Figure 1.** Necrosis Ulcer on LEGV according to Forrest I b

Post endoscopy, on the second and third day of treatment the patient was in fairly well condition, without complaints and there was no hematemesis or black stool. The patient's vital signs were as follows: blood pressure of 110/65 times per minute, heart rate of 65 times per minute, breathing frequency of 18 times per minute, and axillary temperature 36.7°. The patient continued receiving the liquid diet of hepatosol via NGT 6x150 cc, transfusion of PRC 1 bag/day up to Hb  $\geq$  9 g/dl, 500 cc of aminofusin liver infusion for every 24 hours, omeprazole pump of 8 mg/hour for 72 hours, 15 cc of sucralfate orally every 8 hours, 20 mg of propranolol for every 8 hours, 600 mg of telbivudine for every 24 hours. On treatment day four post endoscopy, the patient unexpectedly suffered from recurrent and uncontrolled massive hematemesis and thus resuscitation and intensive care were carried out. The patient later died of uncontrollable bleeding.

### 3. DISCUSSION

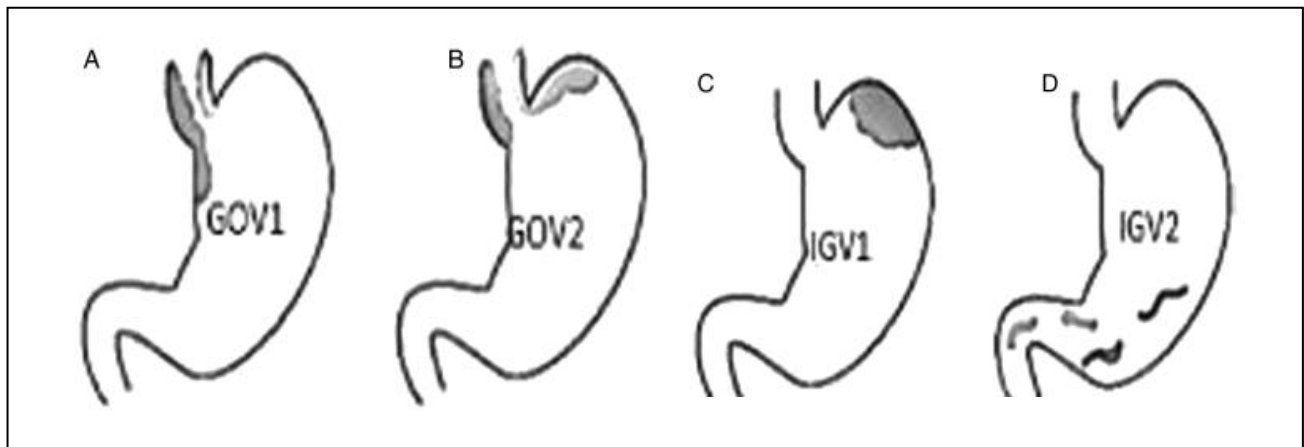
In compensated cirrhosis, the prevalence of gastroesophageal varices ranges from 0–40%. The annual incidence and progression of these cases are estimated to be 7%. In the first year, tiny varices have a 5% bleeding rate, whereas large varices have a 15% bleeding rate. In patients with advanced liver diseases (Child B or C), large varicose veins and varicose veins with red wale marks have a poor prognosis and are associated with high bleeding risk. Mortality was between 15 and 20% at 6 weeks varied and was largely dependent on the severity of liver disease (0% in Child A and 30% in Child C). The incidence of rebleeding after the first bleeding is approximately 60% [3].

*The patient was first known to have suffered from advanced liver disease with Child B liver cirrhosis and the bleeding incident was the patient's first episode. The late diagnosis happened because the patient has never had a medical examination done at a health facility before. The mortality was thought to be caused by massive bleeding related to bleeding complications experienced by the patient.*

Portal hypertension in liver cirrhosis is caused by anatomic changes and the formation of contractile elements in the secondary hepatic vasculature. Both factors are preceded by progressive liver fibrosis and the formation of regenerative nodules. The increase in portal pressure will trigger splanchnic vasodilatation, increased cardiac output, and salt/fluid retention leading to hyperdynamic circulation and increased portal blood flow. Consequently, collaterals form between the portal and systemic systems found between the lower esophagus and the cardiac area of the stomach (gastroesophageal varices). This collateral formation is secondary to lower portal pressure but causes rupture and bleeding risks [3].

Clinically significant portal hypertension occurs when the hepatic venous pressure gradient (HVPG) is above 10 mmHg and can therefore be used as a prognostic marker for complications such as upper gastrointestinal bleeding from gastroesophageal varices, portal hypertensive gastropathy, ascites, spontaneous bacterial peritonitis, syndrome hepatorenal, splenomegaly, hepatocellular carcinoma, and hepatic encephalopathy. Variceal bleeding is less likely to occur when the HPVG is less than 12 mmHg. On the contrary, when the HPVG pressure is above 20 mmHg, the possibility of failure to control bleeding is very high and increases mortality risk [4].

Gastric varices are classified based on their relationship to esophageal varices and their site in the stomach. Gastric varices are divided into gastroesophageal varices, type 1 (GOV1) and type 2 (GOV2). GOV1 is characterized by the esophageal varices extending to the cardia or the minor curvature and are considered as extensions of esophageal varices. Meanwhile, GOV2 (fundal and esophageal varices) tend to be longer and more tortuous. Isolated gastric varices (IGV) may be located in the fundus (IGV1) or anywhere in the stomach (IGV2). The likelihood of bleeding from stomach varices is relatively modest (10-36%) yet tends to turn out severe, requires more transfusion, and has a higher mortality rate compared to bleeding from esophageal varices [1,5].



**Figure 2.** Anatomy of Gastric Varices Based on Their Anatomical Location (A) GOV1: type 1 gastro-oesophageal varices (B). (A) GOV2: type 2 gastro-oesophageal varices (C) IGV1: type 1 isolated gastric varices. (D) IGV2: type 2 isolated gastric varices [1].

An EGD performed on the patient detected grade II-III esophageal varices and varices in the gastric fundus. Endoscopic injection of tissue glue (histoacryl) was performed as an initial treatment to control acute variceal bleeding.

Traditionally, a liver cirrhosis diagnosis is followed by a screening for gastroesophageal varices. However, according to Baveno's VI consensus, screening is not essential in patients with compensated cirrhosis if the transient elastography (TE) value is less than 20 kPa and the platelet count is greater than 150,000/mm<sup>3</sup>. However, if there is evidence of decompensated cirrhosis, the patient should undergo annual screening regardless of the presence of varicose veins. Patients with compensated cirrhosis and known to have varicose veins should be screened every 1-2 years, whereas those with compensated cirrhosis but without varicose veins are to be screened every 2-3 years [4,6].

The gold standard for screening is esophagogastroduodenoscopy (EGD). The main disadvantages of EGD include the fact that it is an invasive procedure that causes discomfort varies from patient to patient, the fact that the diagnosis and classification of varicose veins, particularly small varicose veins, can differ depending on the technician, and the relatively high cost. If esophageal varices are discovered during endoscopy, they should be documented and characterized as follows: Grade I: Collapses when the esophagus is inflated with air; Grade II: Varicose veins that aren't classified as Grade I or Grade III; and Grade III: Varicose veins that occupy more than half of the lumen [4].

The second most prevalent cause of gastrointestinal bleeding is esophageal varices, which have a high mortality rate. Predisposing and precipitating factors for variceal hemorrhage are still not fully established. Some of the factors thought to play a role include the pressure within the varicose veins, the size of the varicose veins, tension in the varicose walls, and the severity of the liver disease [7]. Furthermore, the treatment procedures used to control the bleeding can result in consequences such as infection or tissue injury, which can raise the risk of rebleeding and death. The patient's condition and the therapy carried out are also further complications due to the patient's underlying diseases or concomitant conditions in the patient [8].

Variceal Band Ligation (VBL) is regarded as an effective conventional therapy in cases of esophageal variceal bleeding. However, this procedure is widely ineffective in cases of gastric varicose veins. This treatment has a moderately low percentage of hemostasis (26-71%), as well as a significant rate of rebleeding (up to 60-90%). Although stomach bleeding is uncommon (approximately 20% of cirrhotic patients), it is more often linked with substantial bleeding, serious consequences, and a high fatality rate. Other treatments, such as endoscopic sclerotherapy, have also been shown to be equally ineffective [8].

In the case of gastric variceal bleeding, the hemostatic modality with a high success rate is injection with Histoacryl tissue adhesive glue (2-N-butyl-cyanoacrylate; B. Braun Dexon, Spangenberg, Germany), transarterial intrahepatic portosystemic shunting (TIPS), and balloon occluded retrograde transvenous obliteration (B-RTO). Histoacryl injection is the most often utilized therapy for acute variceal bleeding with TIPS, with B-RTO being performed subsequently if it fails. The inclination for Histoacryl injection is mostly owing to contraindications resulting from the presence of liver illness, which impairs the efficacy of TIPS and B-RTO, as well as the inconvenient nature of conducting these two procedures in a clinical emergency care situation. Thus, the available clinical evidence suggests that endoscopic obliteration of varices using N-butyl-2-cyanoacrylate is good first-line therapy for variceal bleeding because other treatment options tend to be limited [1,8].

The patient's first variceal bleeding episode was presented with red bloody vomitus and black stool for a month before the patient was admitted to the hospital. When the patient underwent the endoscopic procedure, bleeding in grade II-III esophageal varices and fundal varices were discovered. It was suspected that the cause was underlying disease due to the advanced stage of liver cirrhosis (Child B) linked with chronic hepatitis B. The patient was administered Histoacryl ® injection to stop the bleeding.

Histoacryl has been widely utilized since its release in 1984, and it has been found to effectively control gastric variceal hemorrhage [8]. Cyanoacrylate is an acrylic resin that, upon contact, bonds to the surface in the presence of water, particularly hydroxide ions, in 5 to 6 seconds and then undergoes exothermic polymerization in 60 seconds. This substance will adhere precisely to the tissue and, in addition to hemostatic properties, will have bacteriostatic properties [9]. When injected into esophageal or gastric varices, the veins are quickly obliterated. This substance's polymerization is independent of blood clotting factors. Within seconds

after contact with physiological fluids, the adhesive will harden, forming a solid cast from the injected vein. Because the lumen of the varicose veins is obstructed, injection with histoacryl, when done appropriately, will reduce bleeding. The adhesive's quick occlusion makes it easier to apply than traditional sclerosing agents. To prevent an early setting of the substance during the process, the adhesive is mixed 1:1 with a radiographic contrast agent (lipiodol) [9].

After the placement has been confirmed, the tissue glue will be injected in a maximum dose of 0.5 ml for esophageal varices and 1 ml for gastric varices. Another distinction between this tissue glue injection and traditional sclerotherapy is that it is only administered intravariceally. There is no consensus on the cyanoacrylate injection technique with major variations in the proportion and volume of cyanoacrylate and lipiodol solutions to be injected [9].

There are several non-randomized research on the usefulness of cyanoacrylate adhesive for stomach variceal hemorrhage, particularly case series. More than 1000 case reports show that active variceal bleeding can be stopped 93-100% of the time, with a rebleeding rate of up to 10%. In a case study of 34 patients who received cyanoacrylate glue as the main therapy for acute variceal bleeding, 93.8% achieved rapid hemostasis via variceal obliteration in 84% of instances. Rebleeding occurred in just 11.8 percent of patients (n=4) within 48 hours, and complications in the form of superior mesenteric vein thrombosis occurred in only one case. Only 2.1% of patients (n=1) did not survive the treatment, whereas 82.4% of patients (n=28) survived to the end of the study [1].

Primary hemostasis was achieved in 95% of patients (n=37) with acute gastric variceal bleeding who received cyanoacrylate glue injection, according to a similar study [10]. Early or continued rebleeding occurred in only 8% (n=3) and 28% (n=10) respectively, and these rebleeding were not life-threatening. There were no notable problems associated with the surgery after a 14-month follow-up [10].

The complications that occur in the use of histoacryl in several evaluations include systemic embolization, organ infarction, visceral fistula, and bacteremia in low numbers, which indicates that this type of therapy is relatively safe and effective [8]. In addition, there were other reported complications such as ulcer formation (0.1%), major gastric variceal bleeding (0.1%), mesentery hematoma, hemoperitoneum, bacterial peritonitis (0.1%), and reports of recurrent and prolonged bacterial sepsis due to embolic clots. Residual clotting of these substances can constitute a source of infection, releasing occasional bacterial colonization in the bloodstream when it breaks down. In the case of recurring infections, tissue glue that remains after more than 24 weeks should be suspected [1].

After the initial endoscopic surgery with tissue glue, a necrotizing ulcer was discovered in the patient. Clinically, there were symptoms of heartburn following the treatment, which were confirmed during endoscopic evaluation in the form of necrotizing ulcers, which were suspected to be the outcome of post-procedure problems.

There are numerous causes of suspected ulcer formation or tissue necrosis after a cyanoacrylate glue injection as an attempt to halt bleeding [11]. Although the volume of agent injected to accomplish obstruction was 1 to 2 ml, in one case report of fundal varicose veins, up to 5 ml was administered, resulting in agent migration and tissue necrosis. The total amount of glue administered reflects the severity of the bleeding, with significant fundal varicose veins requiring 5 to 10 ml of the agent and numerous injections, increasing the risk of complications. Paravariceal injection (not in varicose veins) is another source of gastric ulcer complications or stomach wall necrosis, especially with large cumulative volumes of histoacryl injection. Conservative and interventional endoscopic therapies are frequently ineffective in treating these complications [11].

In some countries, endosonographic-endoscopic ultrasonography (EUS) or fluoroscopic guidance is indicated to lessen the risk of these problems, albeit it is not yet widespread practice. In gastric variceal puncture, endoscopy with real-time ultrasound guidance can provide a higher level of safety. Reducing the histoacryl volume to an appropriate amount is another intervention that can be done. EUS can also be used to monitor for the possibility of future bleeding [1].

#### 4. CONCLUSION

We present the case of a patient with acute variceal bleeding caused by hepatitis B-associated hepatic cirrhosis who underwent an endoscopic tissue glue injection operation with Histoacryl to stop the bleeding. Following the procedure, the patient had problems in the form of necrotizing ulcers. Histoacryl injection is a treatment that has a high success rate and few side effects for stopping acute gastric variceal hemorrhage. However, procedure-related complications were still a possibility.

#### CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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