

Gastric Variceal Bleeding: The Efficacy and Safety of N-Butyl-2-Cyanoacrylate Glue Injection

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Abstract

Aims: To assess N-2-butyl cyanoacrylate injection's effectiveness and safety in the treatment of gastric varix hemorrhage. Methods: Endoscopic treatment with N-Butyl-2-cyanoacrylate injection was performed on 32 patients (21 males and 11 females) with gastric variceal bleeding. The socioeconomic status of the patients, initial hemostasis, rebleeding rate, complications, and mortality rate were all reviewed retrospectively. Patients with liver cirrhosis who presented with hematemesis or melena or whose endoscopy revealed gastric variceal bleeding were included. Therefore, patients with hemodynamic instability were excluded. Results: A total of 32 patients underwent Histoacryl[®] glue injection to treat bleeding gastric varices. The mean age was 56.09 \pm 9.29 (mean \pm SD) years old. Viral hepatitis is the leading cause of chronic liver disease, both hepatitis B and C accounted for 11 cases (34.4%). IGV1 was the most commonly seen, according to the Sarin classification, with 15 cases (46.8%), followed by GOV1 with 10 cases (31.3%) and GOV2 with 7 cases (21.9%). With 15 cases (46.9%), the majority of patients had a Child-Pugh (CTP) B score. 12 cases (37.5%) and 11 (34.4%), respectively, of hematemesis and melena, were reported. In all patients, initial hemostasis was achieved, and there was no documented complication rate. Conclusion: Given the higher rate of hemostasis and great results, our study's findings indicate that the injection of N-butyl-2-cyanoacrylate under endoscopic guidance is safe and effective in the management of GV hemorrhage. After the initial injection, hemostasis was achieved in all of our patients.

Keywords

Upper Gastrointestinal Bleeding, Portal Hypertension, Gastric Varix, Initial

Hemostasis, Cyanoacrylate (Hystoacryl) Injection

1. Introduction

About 50% of patients with liver cirrhosis have gastroesophageal varices (GOV). Less frequently occurring than esophageal varices (EV), gastric varices account for 10% to 30% of GOV bleeding [1] [2]. Unless they bleed, GOVs typically have shown no symptoms. Hematemesis and/or melena, hematochezia, and possibly non-exterior bleeding are symptoms of variceal hemorrhage. Bleeding was suspected or considered to arise from FV (Fundal Varix) if one of the following criteria was present: 1) active bleeding from the GV was seen; 2) the presence of a clot or an ulcer over the FV; 3) occurrence of bleeding in the context of large FV in the absence of EV or other causes of upper GI bleeding. Meanwhile, rebleeding occurs in 35% to 90% of patients with gastric variceal bleeding (GVB), and GVBs typically have greater fatality rates and are more severe. Depending on the severity of the underlying condition, the size of varix, and the existence of signs that indicate bleeding, the mortality and morbidity rates range between 30 and 50%. Similar to the treatment for EV, endoscopic band ligation (EBL) is favored over sclerotherapy for GOV1 due to a lower risk of complications. However, due to high rates of rebleeding and the possibility of catastrophic bleeding from significant treatment-induced ulcers, EBL and sclerotherapy may not be viable treatments for fundal varices (GOV2 and IGV1). After the finding of Cyanoacrylate (glue), the management of GVB was updated. The tissue glue N-butyl-2cyanoacrylate is a watery solution, which polymerizes and hardens within 20 seconds in a physiological milieu and instantaneously upon contact with blood. This makes it potential for obliterating vessels and controlling bleeding. Cyanoacrylate (glue) injection is recommended for first-line therapy for GVB with the initial control of bleeding in 90% to 100% of patients and rebleeding rates < 15% in the recent series [3] [4]. However, it is not widely used by all the countries in the world. Therefore, in this study, we have retrospectively reviewed the N-2-butyl cyanoacrylate injection's effectiveness and safety in the treatment of GVB at Khmer-Soviet Friendship Hospital, Cambodia.

2. Patients

This study involved 32 patients registered in the documents and meet the inclusion criteria of our study including age, the presence of hematemesis or melena or both with underlying history of chronic cirrhosis, the presence of esophagogastric varices bleeding identified by endoscopy at Khmer-Soviet Friendship Hospital, Cambodia, between January 2021 and June 2022. There were 21 male patients (65.6%) and 11 female patients (34.4%), 100% of Cambodian, aged 40 -71 years old, and the mean age of 56.09 years old.

All the patients were found to be successful with a mean number of 1 session of Histoacryl[®] glue injection. Endoscopic obliteration was done in 31 cases re-

quiring 1 session while only one patient needed 3 sessions to get obliterated because the varices found in that patient were too large.

3. Methods

All patients were moved to the endoscopic room for the procedure after stabilization via IV hydration, blood transfusion, somatostatin, or occasionally with Linton tube compression. A large channel endoscope (Olympus C, Tokyo, Japan) and a disposable injectable 21-gauge needle catheter were used to administer Histoacryl[®] (diameter 0.8 mm, length 8 mm). In a ratio of 0.5 to 0.8 ml, Histoacryl[®] and Lipiodol (Guerbet, Aulnay-Sous-Bois, France) were combined. Senior gastroenterologists performed the majority of procedures while being supervised by knowledgeable staff. Before inserting the catheter, lubricant was pumped through the endoscopic suction channel. The endoscope was used to introduce the preload sclerotherapy catheter into the stomach, and the gastric varix was inserted directly with the needle. In order to reduce the possibility of needle embedment, Lipiodol was administered through the catheter to distribute the glue mixture into varix. The needle was then removed while the glue was still flowing. After that, sterile water was used to cleanse the catheter. Per injection, typically 1 ml of a lipiodol and Histoacryl[®] mixture was given. Repeated injections were given until the stomach varices seemed to occlude, as determined by blunt probe probing. General anesthesia was used for all of the patients. In three days, one month, and six months, the treatment was repeated. We consider it as Early re-bleeding if it occurred within 30 days after the index procedure and as Late re-bleeding if it occurred after 30 days. Based on Sarin et al., gastric varix is classified by their anatomical location seen on the endoscopy [3]. It differentiates gastroesophageal varices (GOV) from isolated GV (IGV). GOV is classified into 2 types respectively, type 1 (GOV1 seen in 70% of GV) is found along the lesser curvature and the cardia, and GOV type 2-mostly along the gastric fundus and may extend to the cardia. IGVs are also classified into 2 types, type 1 is located in the fundus, and type 2 is distal GV or those located at other sporadic locations (see Figure 1 and Figure 2). For all practical purposes, true GV or cardio-fundal varices are the GOV2. The size of these varices, the presence of surface red marks, and the severity of underlying liver disease (Child Turcotte Pugh Score) are predictive of bleeding. This raises the issue of prophylactic intervention for incidentally discovered gastric varices, although this question has not yet been fully answered: very little data exists to determine the risk and benefit ratio of preventive intervention.

4. Statistical Analysis

Program SPSS version 25.0 was used for assisting the quantitative analysis, and descriptive and comparative statistics.

5. Ethical Consideration

All collections of data were made only after an agreement between the Khmer-



Figure 1. Classification of gastric varix according to their location within the stomach. GOV-1: Gastroesophageal varix type 1, GOV2: Gastroesophageal type 2, IGV1: Isolated gastric varix type 1, IGV2: Isolated gastric varix type 2 [5].



Figure 2. Technique of cyanoacrylate glue injection [5].

Soviet Friendship Hospital and the University of Health Sciences, Phnom Penh, Cambodia. The patient's identifications are not shown.

6. Results

All patients with bleeding gastric varices had endoscopic N-butyl-2-cyanoacrylate injections. The baseline Characteristics of our patients are shown in **Table 1**. The patients selected were aged from 40 to 71 years. The mean age was 56.09 years with a standard deviation of 9.29. We found that the majority of patient

Effective	No. of patient	%
Total	32	100
Males/Females	21/11	65.6/34.4
Age, years (mean ± SD)	56.09 ± 9.29	
Etiology of liver cirrhosis		
1) Viral hepatitisB	6	25
2) Viral hepatitis C	2	8.3
3) Alcoholism	9	37.5
4) Non-alcoholism nor viral hepatitis	2	8.3
Bleeding manifestation		
- Hematemesis	12	37.5
- Melaena	11	34.4
- Both	9	28.1
Child-Pugh Classification (A/B/C)	9/15/8	28.1/49.9/25
Gastric varix form		
- GOV1	10	31.3
- GOV2	7	21.9
- IGV1	15	46.9
- IGV2	0	0
Association with Hepatocellular carcinoma	5	15.6

 Table 1. Baseline characteristics of patient with gastric variceal bleeding treated with

 Histoaryl glue injection.

lives in a province with 24 patients (75%), while 8 patients (25%) live in Phnom Penh. Most of the patient who comes to the hospital with the bleeding presentation of hematemesis accounted for 12 cases (37.5%) followed by melena with 11 cases and both hematemesis and melena with 9 cases (34.4% and 28%), respectively.

The blood test result characteristic of all 32 patients was demonstrated in **Table 2**. The gastric variceal bleeding was found to be caused by portal hypertension in decompensated liver cirrhosis with various etiology. We noted that the two most common causes of chronic liver disease were related to viral hepatitis, HBV and HCV with 11 cases (34.4%) each, followed by alcohol with 8 cases (25%) and non-alcohol nor viral hepatitis with 2 cases (6.2%) (see **Figure 3**). All 32 patients enrolled were found to be successful with a mean number of 1 session of injection. The endoscopic obliteration was done in 31 cases requiring 1 session while only one patient needed 3 sessions to get obliterated because the varices found in that patient were too large. The average volume of Histoacryl[®] and Lipiodol combined calculated was in a ratio of 0.5 to 0.8 ml, initial hemostasis and completed variceal obliteration were achieved in all patients (see **Table 3**). Rebleeding in our study was defined by the presence of hemorrhage signs:

Blood test result	Mean ± SD	
Hemoglobin (g/dL)	8.17 ± 2.16	
Platelets (K/µL)	137.87 ± 89.94	
Prothrombin (%)	54.69 ± 20.56	
Creatinine (mg/L)	10.2 ± 2.92	
Total bilirubin (mg/dL)	2.47 ± 3.23	
ALT/AST (IU/L)	$46.41 \pm 44.70/85.53 \pm 64.15$	
Albumin (g/L)	29.41 ± 2.97	
Transfusion (number of pack)	1.81 (0 - 6 packs)	
Glycemia (mg/dL)	167.84 ± 96.60	

 Table 2. The blood test results of 32 patients treated with N-butyl-2-Cyanoacrylate glue injection.

 Table 3. Number of sessions and volume of Histoacryl injection.

Number of sessions	Number of patients	
1	31	
3	1	
Mean number of sessions	1	
Average volume of Histoacryl	0.5 ml	



Figure 3. The etiologies of liver cirrhosis.

hematemesis or melena or hematochezia or decreased hemoglobin level > 2 g/dL within 5 days of hospitalization after glue injection. All 32 patients treated with N-bulyl-2-cyanoacrylate injection failed to face any rebleeding event. Embolism is the most concerning complication in the treatment of gastric varices with N-2-Butyl Cyanoacrylate. Fortunately, we didn't find any case of thromboembolism. Anyway, we noticed that there was one case of fever 48 h after injection but resolved spontaneously without any infectious source finding (see Figure 4). We also found that there was no case of death after glue injection therapy with Histoacryl[®]. All patients were discharged. We considered that among patients hospitalized, an average blood pack for transfusion was 1.81 packs ranging from 0 to 6 packs of red blood cells.



Figure 4. The complications of cyanoacrylate glue injection.

7. Discussion

GVs were less frequently found than esophageal varices in asymptomatic portal hypertensive individuals who underwent endoscopic monitoring for varices (EVs). Although there is a lower chance of GVs bleeding, it is nonetheless severe and sometimes fatal [3]. Mortality rates for the initial variceal hemorrhage range from 20% to 30% percent, and for the second occurrence, they can approach 50%. Recurrence of bleeding is observed in 30% of patients within the first 6 weeks of the first episode and in about 70% during the following year [3] [6]. The reported rebleeding rate after Histoacryl[®] injection for acute gastric variceal bleeding ranged from 22% - 59% [7]. Apart from band ligation and Cyanoacrylate injection (Histoacryl[®]), Balloon-Occluded Retrograde Transvenous Obliteration (BRTO) is a very effective technique in temporarily controlling bleeding with immediate action in 80% of patients [7]. Unfortunately, its use is associated with potentially lethal complications such as aspiration, migration, and necrosis/perforation of the esophagus with mortality rates higher than 20%. Therefore, it should be restricted to patients with uncontrollable bleeding for whom a more definitive therapy (e.g TIPS) is planned within 24 hours of placement. It is strongly recommended for airway protection when balloon tamponade is used [8] [9]. Transjugular Intrahepatic Portosystemic Shunt (TIPS) is widely used as a salvage therapy for GV bleeding and is increasingly used as first-line treatment, especially in the United States and Europe while BRTO remains more commonly used in Eastern countries. TIPS was first shown to be successful for GV bleeding in a 1998 study that showed outcomes for TIPS in acute GV versus OV bleeding were equal with hemostasis being achieved in all but one patient. Re-bleeding occurred in 4/28 patients due to shunt thrombosis or occlusion, which the authors report was easily diagnosed and managed. The study, therefore, established the role of TIPS as a rescued procedure in the management of uncontrolled GV bleeding [4]. However, Cyanoacrylate (glue) injection is still recommended for first-line therapy for GVB [3] [10] with the initial control of bleeding in 90% to 100% of patients and rebleeding rates < 15% in recent series [11] [12]. The mean age of the patients in our study was 56.09 years. This finding might be aligned with numerous studies in the literature, where viral hepatitis was primarily the cause of chronic liver disease because it took the disease more than two decades to progress from a healthy liver to a decompensated liver and cause gastric varices [13] [14] [15] [16] [17]. A series by Seewald S, et al. conducted in Germany and Egypt in 2008 [11], a study by Muhammad M, et al., a study conducted by Jun CH, et al. in 2014 in Korea [18], and the study conducted by Lean Sopheak in Cambodia in 2017 [19] found the mean age: 57.2 years old, 57.65 years old and 59.6 years old respectively. Our study's sex distribution was primarily in male patients with a sex ratio of 2:1, which was similar to research done by Seewald S. et al. in Egypt and Germany in 2008 [11] and by Noophun P. et al. in Thailand in 2005 [16]. According to the study conducted in Taiwan region in 2000 by Huang YH, et al. [20], the sex ratio was 4:1 which was significantly different from our result with a sample size of 90 cases (78% were male and 22% were female). We noticed that study was carried out for 6 years from 1992 to 1998 with a total sample size of 893 patients and lately selected only 90 patients with bleeding from gastric varices. Viral hepatitis was the leading cause of chronic liver disease with 67 cases (74.5%). So, dominance in men and viral hepatitis in this series could be explained by the low quality of public health during that period and unprotected sex for male patients. Gastroesophageal varix type 1 is the most prevalent kind reported in the literature, making up 74% of all GV. However, IGV 1 and GOV 2 have the highest rates of bleeding, respectively [21]. The majority of fundal varices (FVs) enter the inferior phrenic vein, which subsequently connects to either the left renal vein to create the gastro-renal shunt (GRS) (80% - 85%) or the inferior vena cava [22]. This is because fundal varices (FVs) consist of GOV2 and IGV1. Many studies have found that the mean hepatic venous portosystemic pressure gradient (HVPG) is lower in fundal varices (FV) compared to esophageal varices (EVs), and this gradient is believed to be caused by the presence of these shunts. However, unlike EVs, a significant proportion of FVs (36.8%) still bleed with an HVPG < 12 mm Hg because of the large size of FV and the resultant higher wall tension [23]. This finding could be explained that GV type IGV1 and GOV2 are the most common type of GV bleeding in many studies. As for initial hemostasis current study's population resulted in a 100% rate which was almost identical to some different studies shown in Table 4. However, the procedure-related complication of Histoacryl® in our study was observed in 3.12% of the overall results which is slightly lower than the local study conducted by San Polen in Cambodia in 2016 with 9.61%

Table 4. The comparison of initial hemostasis in different studies.

Author	Country	Year	Initial hemostasis (%)
Current study	Cambdia	2022	100
Seewald S, et al. [11]	Germany and Egypt	2008	100
Chang YJ, et al. [27]	Korea	2009	100
Prachayakul V, <i>et al.</i> [25]	Thailand	2013	97.8
Jun CH, <i>et al.</i> [18]	Korea	2014	96.9

[24] and is lower than one study in Thailand done by Prachayakul V, et al. in 2013 with 13.9% [25]. Systemic embolization is a serious side effect of N-butyl-2-cyanoacrylate injection (NBCA). According to a study, NBCA glue can have embolic side effects such as stroke as a result of thromboembolism in the anterior or posterior circulation, pulmonary embolism (PE), splenic embolism, or portal vein thrombosis. It may also cause multi-organ infarction in the presence of patent foramen ovale or the presence of any arteriovenous (AV) pulmonary shunt [23]. Fortunately, there is no case of complication related to thromboembolism event found in our study. This is similar to the study of Prachayakul V, et al. in Thailand which showed there is no complication of embolism in all 90 cases receiving therapy with Histoacryl[®] [25]. The absence of death cases could be explained by the standardized technique adopted in our study. Fever is the only complication related to Histoacryl[®] sclerotherapy in the current study accounting for 3.12% but it was resolved spontaneously without any source of infection noticed within 48 h. This may not be of clinical impact if it is only a matter of transient bacteremia. In addition, the current standard of care for cirrhotic patients with GI bleeding already includes prophylactic antibiotics to prevent bacterial infections [26].

8. Conclusion

Gastric variceal bleeding represents numerous complications of chronic liver disease, known as cirrhosis. Men are mostly affected than women. The most affected age group ranges between 40 and 71 years old. The most frequent clinical symptom of gastric variceal bleeding is hematemesis. The endoscopic aspects findings are gastric varix type IGV1. Viral hepatitis is the leading cause of liver cirrhosis. No complication related to glue injection was noted in our series. Our study result demonstrated that the injection of N-butyl-2-cyanoacrylate with endoscopic guidance is safe and effective in the management of GV bleeding due to a higher rate of hemostasis and excellent outcome. 100% of our patients got hemostasis after the initial injection.

Authors' Contributions to the Manuscript

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: SOU, MEAS, NOV, UONG, EK, CHEY.
- Drafting the article or revising it critically for important intellectual content: SOU, UNN, CHEY, NY, CHHIT, KHUON.
- Final approval of the version to be published: SOU, MEAS, EK, UNN, NOV, KANG, UN, KAING, KHUON, NY, MON, KANN, CHHIT, UM, CHEY.
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: SOU, MEAS, EK, UONG, CHEY, UNN, NOV, KANG, UN, KAING, KHUON, NY, MON, KANN, CHHIT, UM, CHEY.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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