Clinical Gastroenterologist International

ISSN: 2691-5642

Research Article

Endoscopic Obliteration with Cyanoacrylate Glue for Gastric Fundal Variceal bleeding: Analyzing Results from a 28-year Experience with an in-House Technique

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Abstract

Objective: Endoscopic obliteration for Gastric Fundal Variceal (GFV) bleeding using cyanoacrylate glue is challenging. The study aimed to assess the safety and favorable short and long-term outcomes of this treatment for GFV bleeding and focused on the relevance, feasibility, and quality of this technique.

Methods: This retrospective study was conducted in 101 patients who received treatment for GFV bleeding at Nagoya Medical Center between August 1992 and May 2019. Following clinical studies, we refined our injection technique to reduce the amount of cyanoacrylate glue diluted with 5% lipiodol (1:1). The entire GFV vessel was filled with the cyanoacrylate glue mixture plus 50% glucose in one or two injections under fluoroscopic monitoring. Results were divided into two periods. The first period (1992-2005) focused mainly on clinical studies. The second period (2006-2019) focused on general practice.

Results: In the second period, rates of primary hemostasis and rebleeding were 97.7% and 9.3%, respectively, which were comparable to those in the first period. Adverse events during the procedures performed in first period rarely occurred in the second period. The median survival time of all patients was 5.5 years, whereas 1-year, 10-year, and 20-year cumulative survival rates were 76%, 26%, and 12%, respectively.

Conclusion: An improved practical approach is necessary to achieve favorable outcomes. The refined in-house endoscopic technique with cyanoacrylate glue for GFV bleeding is highly efficient and results in favorable clinical and prognostic outcomes.

Keywords: Endoscopic obliteration; Histoacryl®; 50% glucose; Lipiodol; Gastric fundal variceal bleeding; Hemostasis; Long-term survival

Introduction

Gastric Varices (GVs) are often detected in patients with portal hypertension [1,2]. However, Gastric Fundal Varices (GFVs) are most often associated with a gastro-renal or gastro-inferior vena cava shunt, potentially causing outflow into the systemic circulation. Furthermore, these anatomical features are associated with high blood flow through the shunt and can cause severe and potentially life-threatening GFV bleeding [1-5]. Noninvasive and simple endoscopic approaches are preferred therapeutic solutions.

Histoacryl® is tissue adhesive butyl cyanoacrylate glue that immediately polymerizes in contact with blood, inducing vascular obstruction. The use of Histoacryl® for endoscopic intravascular injection was originally advocated as a therapeutic option for bleeding of large esophagogastric varices in 1986 [6]. Subsequent studies have indicated that this method might be beneficial in obliterating GVs and it has been successfully applied in general practice worldwide for the treatment of GV bleeding [7-10]. However, despite reported success rates, rebleeding rates ranging from 23% to 40% have also been reported, and there remains controversy regarding optimal techniques, [7-11] adverse events, [11-15] and favorable long-term outcomes associated with this treatment [7]. In 1990, we introduced endoscopic Histoacryl® injection for GV obliteration. In addition, by using Endoscopic Ultrasonography with color Doppler imaging (EUS-CD), we analyzed GV hemodynamics and the polymerization of Histoacryl® when mixed with lipiodol during and after treatment [16-18]. The mixture solidified and produced GV occlusion in a few minutes, but the region not completely solidified was prone to rebleeding. We reported that a mixture of Histoacryl® and lipiodol in a 1:1 ratio was appropriate to fill the entire GV under fluoroscopic monitoring [17-18].

From 1992 to 1999, we conducted a prospective clinical study of this new preparation for GFV bleeding. In that study, GFV anatomy was investigated using EUS-CD before treatment and was verified using varicography after treatment [19]. GFV anatomy could be broadly divided into two types. Type 1 consisted of a single varicose vessel of almost the same diameter as the inflow/outflow vein, whereas type 2 consisted of multiple varicose vessels with complex connecting ramifications. After our clinical study, we refined the injection technique to reduce the necessary volume of the Histoacryl® mixture per intervention and implemented this technique to treat GFV bleeding in general practice.

In this study, we presented validated results from a 28-year experience with the endoscopic injection technique, which was modified to be more efficient and safer. The primary focus was to achieve longer patient survival rates attributable to the favorable features of this endoscopic procedure in managing GFV bleeding.

Citation: Iwase H, Shimada M, Hirashima N, Saito M, Kondo H, Urata N, et al. Endoscopic Obliteration with Cyanoacrylate Glue for Gastric Fundal Variceal bleeding: Analyzing Results from a 28-year Experience with an in-House Technique. Clin Gastroenterol Int. 2020; 1(1): 1007.

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Publisher Name: Medtext Publications LLC

Manuscript compiled: Mar 24th, 2020

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Methods

Patient assessment

Our gastroenterology department has been offering endoscopic obliteration with Histoacryl® for GV bleeding since 1990 and it is a regional referral center for patients requiring this treatment. For the present study, we retrospectively reviewed the treatment outcomes of 101 patients who received treatment for GFV bleeding between August 1992 and May 2019. GFV lesions were divided into two types according to location: (1) the localized-type, located in the fundus with clear margins, and (2) the diffuse-type, located in the area from the fundus to the cardia. GFV lesions extending from obvious Esophageal Varices (EV) were excluded in this study. The GFV-forming vessels were divided into types 1 and 2 based on varico graphic findings after treatment [19]. Rates of hemostasis, rebleeding, and adverse events over 28 years were divided into two periods. The first term (1992-2005) focused primarily on clinical work, whereas the second term (2006-2019) focused on general practice.

Procedures

All endoscopic and related procedures were performed by experienced professional gastroenterologists or endoscopists. N-butyl cyanoacrylate (Histoacryl®; B. Braun Melsungen, Melsungen, Germany) was diluted with 5% lipiodol (1:1) before injection. Endoscopic injection of the Histoacryl® mixture was performed with a forward-view video endoscope by using a 22 or 23-gauge endoscopic injection needle with a sheath (Top. Co., Ltd., Tokyo, Japan). The GFV was carefully punctured to avoid intramural injection. In clinical settings, the Histoacryl® mixture was rapidly injected into the GFV, which was followed by slow injection under fluoroscopic observation [19].

The first injection was stopped when the Histoacryl® mixture moved from the puncture site to the juxta-variceal portions of the inflow/outflow veins. Following the clinical work, the injection technique was modified to reduce the necessary volume of the mixture; 2 mL of the mixture (approximately 1 mL for tortuous GFV) was initially injected (Figure 1a, b) and was immediately followed by flushing with 50% glucose into the GFV (Figure 1c). The injection of the Histoacryl® mixture resulted in mass polymerization and effectively occluded the GFV vessel. The incompletely polymerized lump was still jelly-like and pliable. The lump was spread from the puncture site to the outflow/inflow vein followed by continuation of the 50% glucose (Figure 1d). The needle was then removed from the GFV (Figure 1e). We planned to completely occlude the GFV in this first session. The adequacy of obliteration was judged by the shape of the Variceal following Histoacryl® administration and by palpation with the blunt sheath of the needle. A non-occluded GFV appeared to be compressible when applying pressure and a second injection could be performed at the non-occluded site (Figure 1f-h). By approximately 6 months, the GFV was obliterated with fibrotic changes and regenerating venules (Figure 1i) [19]. EUS-CD was performed for undetectable non-occluded GFV [17]. However, most GFV lesions consisted of a single varicose vessel and could be effectively occluded with 1 or 2 injections (Figure 2a, b).

In the case of diffuse-type GFV, the remaining varicose vessels and connecting ramifications were occluded in one or two injections of the Histoacryl® mixture following occlusion of the main varicose vessel. When a clear endoscopic view could not be obtained because of food or extensive GFV bleeding, the patient was instructed to lie on their right side. This maneuver aided in displacing the remaining food or blood flow and allowed a clear field of view of the punctured GFV. A Linton tube was used to achieve transit hemostasis if a good view was not obtained or an experienced doctor was absent. On the day after treatment, we conducted blood chemistry, chest radiography, and urine test to evaluate adverse events. Within 1 week, endoscopy and chest-abdominal Computed Tomography (CT) scans were performed.

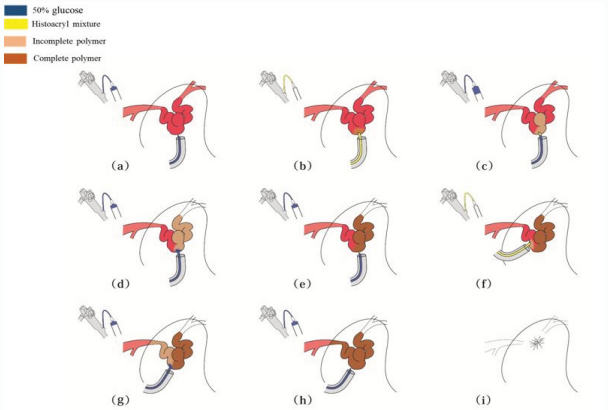

Figure 1: Endoscopic Histoacryl® mixture and 50% glucose solution injection in managing Gastric Fundal Variceal (GFV). (a) The exact position of the needle relative to the planned GFV puncture site was verified before puncturing. (b) Just after puncturing, 2 mL of the Histoacryl® mixture is immediately injected followed by flushing with 50% glucose to produce an incomplete polymer mass in the GFV (c). (d) The polymer mass is spread from the puncture site to the outflow/inflow vein by continuing to inject 50% glucose. (e) The needle is removed from the GFV and an incomplete polymer mass becomes completely polymerized. (f) A second puncture is made at the non-occluded site. The amount of Histoacryl® mixture in the second injection is approximately half the initial injection. (g) The polymer is then spread from the puncture site to the non-occluded vessel by continuing to inject 50% glucose. (h) The needle is removed and the GFV is occluded with the polymerized mixture. (i) By roughly 6 months, the GFV is completely obliterated with fibrosis including the outflow/inflow vein.

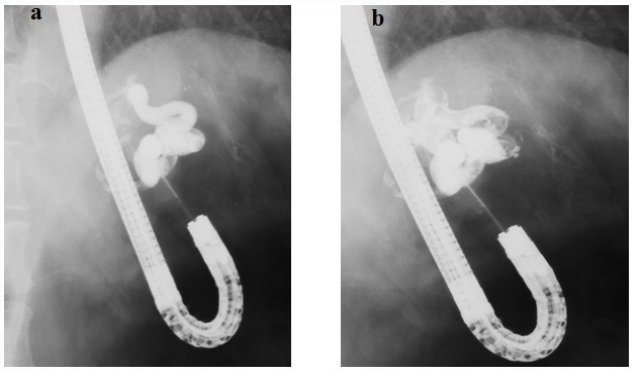

Figure 2: Varicography of localized-type GFV bleeding during treatment. (a) Varicography during the first injection showing the Histoacryl® mixture and 50% glucose solution occluding the puncture site to the outflow/inflow vein. (b) Varicography during the second injection showing the Histoacryl® mixture and 50% glucose solution completely filling the GFV.

Follow-up endoscopic surveillance was conducted at 3 and 6 months after the first procedure and every 6 months thereafter until GFV was obliterated. Endoscopic injection with Histoacryl® was attempted in the event of rebleeding or GFV re growth. Patients who developed EV or EV bleeding underwent conventional endoscopic therapy.

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Ethical considerations

The requirement for acquisition of written informed consent from patients was waived owing to the retrospective nature of this study. The Ethical Review Committee of National Hospital Organization Nagoya Medical Center approved this study on April 9, 2019 (approval number 2018-097). This study was conducted in accordance with the guidelines set out by the Declaration of Helsinki.

Statistical analyses

Where appropriate, the numerical results are expressed as medians (range). Chi-squared test was used to compare differences between categorical variables. Patients were followed up until death or May 10, 2019. Kaplan-Meier survival curves were constructed to show survival time and were compared using generalized Wilcox on and log-rank tests. Significant level was set at P<0.01.

Results

Patient demographics

Clinical features and demographics of the 101 patients in this study, divided into two groups with localized-type GFV (n=42) and diffuse-type GFV (n=59), are summarized in Table 1.

Hemostasis of GFV bleeding and rebleeding

Table 2 presents hemostasis in GFV bleeding. Successful primary hemostasis was defined as the absence of recurrent bleeding within 48 h, whereas complete success was defined as the absence of recurrent bleeding for at least 1 month after achieving initial hemostasis. The success rates of complete hemostasis for localized-type GFV bleeding were 100% in both the first and second periods. As for diffuse-type GFV, two patients in the first period and one patient in the second period did not achieve primary hemostasis, and the complete hemostasis rates were 89.5% and 90.5% in the first and second periods, respectively (Table 2).

Table 1: Demographic features of the 101 patients in this study.

Demographic/endoscopic features	Localized-type (%)	Diffuse-type (%)	Total
Number of patients in subgroups	42	59	101
Emergent/elective	16/26	28/31	44/57
Median age, year (range)	65 (41-84)	63 (36-84)	64 (36-84)
Male/female	25/17	37/22	62/39
Etiology of portal hypertension			
Cirrhosis	37 (88.1%)	51 (86.4%)	88 (87.1%)
Viral hepatitis B	4 (9.5%)	5 (8.5%)	9 (8.9%)
Viral hepatitis C	21 (50.0%)	28 (47.5%)	49 (48.5%)
Alcohol abuse	9 (21.4%)	14 (26.9%)	23 (22.8%)
Other	3 (7.1%)	4 (6.8%)	7 (6.9%)
Non-cirrhotic	5 (11.9%)	8 (13.6%)	13 (12.9%)
Child-Pugh class (A/B/C)	8/13/2021	12/17/1930	20/30/51
Hepatocellular carcinoma			
(+)	6 (14.3%)	11(18.6%)	17 (16.8%)
(-)	36 (85.7%)	48(81.4%)	84 (83.2%)
Vascular anatomy			
Type 1	38 (90.5%)[a]	36 (61.1%)	74 (73.3%)
Type 2	4 (9.5%)	23 (39.0%)	27 (26.7%)

[a]P<0.01 *vs.* diffuse-type

Table 3 shows rebleeding rates. Rebleeding was defined as early (i.e., within 30 days of primary hemostasis) and late (i.e., after 30 days). During the follow-up period, early rebleeding from localized-type GFV did not occur in either the first or second period. With respect to localized-type GFV, late rebleeding occurred in two patients but was followed by complete hemostasis after endoscopic Histoacryl® injection. As for diffuse-type GFV, late rebleeding occurred in four patients in the first period and three patients in the second period. In two patients, the remaining small varicose vessels in the submucosa, which were undetectable with standard endoscopy but detectable with EUS-CD, bled (Figure 3a, b). In these cases, complete hemostasis with endoscopic Histoacryl® injection was achieved (Figure 3c, d). Two patients experienced stomach devascularization following splenectomy, and one patient showed partial splenic artery embolization due to failure of endoscopic Histoacryl® reinjection over three times to induce complete hemostasis. In the diffuse-type GFV subgroup, three patients died of severe EV bleeding.

EV and GFV rebleeding did not occur in survivors after 5 years following initial treatment for GFV bleeding. Bleeding due to portal hypertensive gastropathy occurred in 6 patients with diffuse-type GFV.

Association of Histoacryl® mixture volume with adverse events

Table 4 shows the volume of the Histoacryl® mixture injected and associated adverse events. During the first term, abdominal pain, fever, and pulmonary embolism were major adverse events but were not severe. Patient recovered from these events without intervention or with conservative therapy. Two patients with localized-type GFV complained of mild, unremitting abdominal discomfort after injection of 5 mL of the Histoacryl® mixture. A CT scan revealed splenic vein embolism in these patients. One of these patients died of liver failure. One patient with diffuse-type GFV developed severe stomach pain and high fever. A CT scan revealed splenic infarction. This patient fully recovered following conservative therapy after 6 months. Two other patients with diffuse-type GFV developed fever at 5 months after injection of 6 and 10 mL of the Histoacryl® mixture, respectively. A CT scan showed the Histoacryl® mixture in the necrotic gastric wall and retroperitoneal abscesses. One of these patients died of sepsis, whereas the other recovered after gastrectomy.

Furthermore, other adverse events, including adhesion of the Histoacryl® glue to the endoscope, a trapped needle in the varices, and needle blockage, were observed during the procedure in a few patients in the first period. The median amount of the Histoacryl® mixture used for localized-type and diffuse-type GFV was 4 and 6 mL during the first term and 2 mL and 3 mL during the second period, respectively. Adverse events that occurred during the first period rarely occurred during the second period.

Patient survival and mortality rates

The survival rate for all patients included in this study over 28 years is presented by a Kaplan-Meier survival curve in Figure 4. During the observation period, 69 (68.3%) patients died. Liver failure was the main cause of death in 37 cases, followed by hepatocellular carcinoma in 13 cases, GFV bleeding (including rebleeding) in 6 cases, EV bleeding in 3 cases, gastrointestinal bleeding in 3 cases, and other causes in 7 cases. Therefore, the Median Survival Time (MST) was 4.9 years, whereas the 1-year, 10-year, and 20-year cumulative survival rates were 76%, 26%, and 12%, respectively. Likewise, the

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Table 2: Hemostasis due to gastric fundal variceal bleeding.

	First term (1992-2005)			Second term (2006-2019)		
	Localized-type *n*=21 (%)	**Diffuse-type *n*=38 (%)**	**Total *n*=59(%)**	**Localized-type *n*=21 (%)**	**Diffuse-type *n*=21 (%)**	**Total *n*=42 (%)**
Primary hemostasis	21 of 21 (100%)	36 of 38 (94.7%)	57 of 59 (96.6%)	21 of 21 (100%)	20 of 21 (95.2%)	41 of 42 (97.6%)
Complete hemostasis	21 of 21 (100%)	34 of 38 (89.5%)	55 of 59 (93.2%)	21 of 21 (100%)	19 of 21 (90.5%)	40 of 42 (95.2%)

Table 3: Rebleeding and hemorrhage after the first treatment.

Variable	First term (1992-2005)			Second term (2006-2019)		
	Localized-type n=21 (%)	**Diffuse-type n=38 (%)**	**Total n=59 (%)**	**Localized-type n=21(%)**	**Diffuse-type *n*=21(%)**	**Total n=42 (%)**
Gastric variceal bleeding	2 (9.5%)	6 (15.8%)	8 (13.6%)	0	4 (19.0%)	4 (9.5%)
3 days to <1 month	0	2 (5.3%)	2 (3.4%)	0	1 (4.8%)	1 (2.4%)
1 month to <12 months	0	3 (7.9%)	3 (5.1%)	0	3 (14.3%)	3 (7.1%)
12 months to <5 years	2 (9.5%)	1 (2.6 %)	3 (5.1 %)	0	0	0
≥5 years	0	0	0	0	0	0
Esophageal variceal bleeding	0	5 (13.2%)	5 (8.5%)	0	3 (14.3%)	3 (7.1%)
1 month to <12 months	0	2 (5.3%)	2 (3.4%)	0	1 (4.8%)	1 (2.4%)
12 months to <5 years	0	3 (7.9%)	3 (5.1%)	0	2 (9.5%)	2 (4.8%)
≥5 years	0	0	0	0	0	0
Portal hypertensive gastropathy	0	4 (10.5%)	4 (6.8%)	0	2 (9.5%)	2 (4.8%)

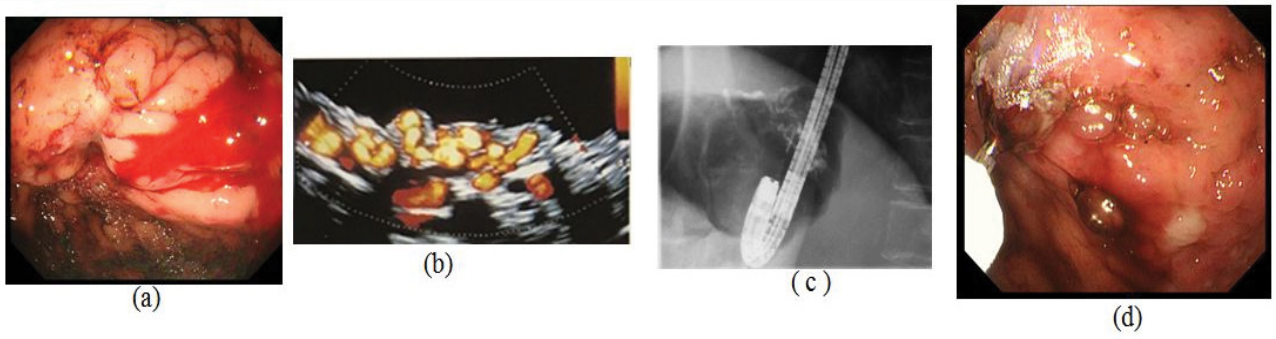

Figure 3: Bleeding from a small varix in the submucosa. (a) Endoscopy showing any blood leakage from the site of GFV obliteration. (b) EUS-CD color flow image of a dilated vessel in the submucosa. (c) Varicography showing the remaining dilated varicose vessel with connecting ramifications in the submucosa filled with the Histoacryl® mixture and 50% glucose. (d) Endoscopic image showing hemostasis of the bleeding point just after the procedure.

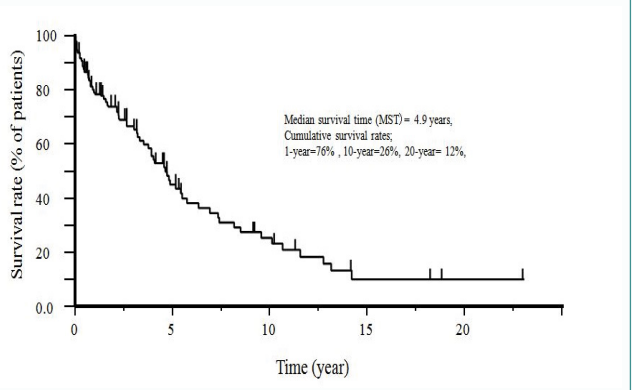

Figure 4: Kaplan-Meier survival curve showing the survival rate with time among all patients after undergoing endoscopic obliteration with Histoacryl® for GFV bleeding. Median Survival Time (MST) was 4.9 years and cumulative survival rates were 76%, 26%, and 12% at 1, 10, and 20 years, respectively.

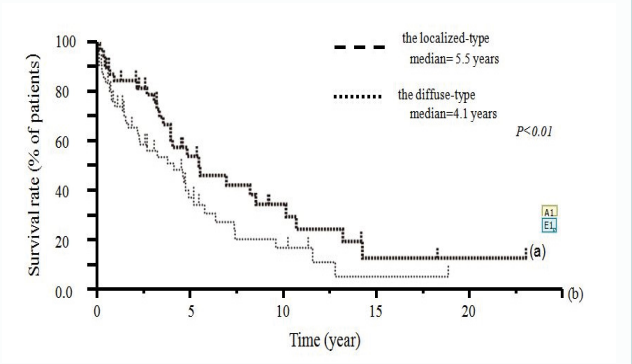

Figure 5: Kaplan-Meier survival curves showing the survival rates with time in patients who underwent endoscopic obliteration with Histoacryl® for (a) localized-type or (b) diffuse-type GFV bleeding.

Kaplan-Meier survival curves in Figure 5 show the survival rates of the patients in the localized-type GFV and diffuse-type GFV subgroups; the MST was 5.5 years and 4.1 years for the localized-type and diffuse-type GFV subgroups, respectively (P<0.001).

Discussion

The fundamental mechanism that results in the occlusion of the entire GFV with a Histoacryl®: lipiodol (1:1) mixture has not changed since it was introduced by our group in 1990 [16-19]. Successful primary hemostasis rates of 96.6% and 97.6% and rebleeding rates of 13.6% and 9.5% during the first and second periods of our 28-year experience, respectively, are comparable to or better than those produced by alternative methods [7-10]. However, some adverse events including severe ones did occur during the first period. We subsequently improved the injection technique and reduced the necessary volume of the Histoacryl® mixture. Accordingly, adverse events rarely occurred during the second period. This retrospective

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study, which analyzed results from our 28-year experience, supported the feasibility of our improved GFV procedure to determine more favorable outcomes.

One aspect of the technique that may increase the risk of failure is accidental puncturing of tissue outside variceal vessels at the injection site with the endoscope needle delivering the Histoacryl® mixture. Other considerations include the quality of the Histoacryl® mixture, which depends on its diluting agent. Using lipiodol as a diluting agent ensures that the glue does not solidify too quickly [6-9,11]. However, diluting Histoacryl® too much prolongs the polymerization process and increases the risk of fragments from the mixture breaking away and distantly embolizing [11-14]. In fact, polymerization of the mixture when it comes in contact with blood in the varicose vessels could be visualized in real time using EUS-CD imaging and fluoroscopic techniques [16-22]. With these considerations, we found that Histoacryl® diluted with 5% lipiodol (1:1) was appropriate in filling the GFV vessels and allows for fluoroscopic monitoring, which is necessary to verify intravariceal puncture, determine the range of vessel occlusion, and locate any embolism [16,19].

The first essential step in our GFV obliteration procedure is to precisely puncture the GFV. The side of the protruding varix in which varicose vessels pile up should be selected for puncturing. Firm puncturing is necessary to pass through thick gastric mucosa. At the same time, deep puncturing should be avoided as this might result in piercing through the GFV. It is, however, necessary to ensure penetration of the needle into the vascularzed varicose vessels of the gastric mucosa.

The next important step is the injection of the Histoacryl® mixture. Understanding the local vascular structure and hemodynamics is important in effectively and safely filling the GFV with the mixture [1-4]. Most GFV sites consist of a single varicose vessel, and a tumorous GFV site may even comprise piled-up single vessels (type 1 vascular) [19]. According to varicographic analysis during and after treatment in this study, type 1 vascular anatomy was present in 73.3% of GFV sites and 90.3% of localized-type GFV sites. If the entrance site of the varicose vein perforating the GFV was blocked with the Histoacryl® polymer, blood flow into the GFV was adequately compromised. In such situations, Romero-Castro et al. [20]. Targeted the entrance site of the perforating veins using EUS-guided injection and blocked it with a small amount of cyanoacrylate glue. However, it was difficult to know if the perforating vein was afferent or efferent, rendering the technique more time-consuming [20-22].

Numerous reports of injected Histoacryl®-related adverse events have been published. Most problems arise from the volume of cyanoacrylate glue used, with larger volumes increasing the risk of adverse events [5-14]. An excessive volume of Histoacryl® resulted in local tissue necrosis, ulcer bleeding, splenic infarction, non-target organ embolization, and needle and endoscope damage [11-15]. Surgical intervention for severe adverse events such as gastric wall necrosis and retrogastric abscess was necessary to prevent their progression to life-threating conditions [15].

A 50% glucose solution would not solidify with cyanoacrylate glue but would still result in hemostasis through an initial osmotic dehydration and sclerosant effect [23,24]. Considering this, we found that continuous injection of a 50% glucose solution resulted in the filling of the entire varicose vessel with the Histoacryl® mixture polymer, from the injection site to the inflow/outflow vein. Likewise, pulling out the needle while continuing the glucose injection helped to remove the needle and endoscope safely without bleeding from the injection site.

After 2006, the median injection volume of the Histoacryl® mixture necessary to fill the entire GFV was 2 and 3 mL for localized-type and diffuse-type GFV, respectively. During the second period, the amount of the Histoacryl® mixture could be reduced to minimize adverse events by adopting additional modifications, such as continuous injection of 50% glucose.

The speed of injection of the Histoacryl® mixture and 50% glucose by assistant medical personnel is also important. An injection that is too slow might result in blockage of the needle and sticky varices, allowing the flow of blood to displace the Histoacryl® mixture. Multiple fatal systemic embolisms following continuous slow injection of cyanoacrylate in bleeding GV have been reported [25]. To form a polymer lump in the varicose vessel, the Histoacryl® mixture should be flushed out quickly. The injection of 50% glucose should be done carefully under fluoroscopic guidance, considering the vascular anatomy of the GFV and the potential presence of a vascular malformation, such as portosystemic spleno-renal or gastro-pulmonary shunts [25]. The movement of the polymer, which is monitored fluoroscopically, depends on the injection speed of the 50% glucose solution. Rapid injection increases the risk of forcing the polymer mass into an unintended site [11-14].

Patients were hopeful of their prognosis if rebleeding was avoided. In the first treatment session, the GFV must be obstructed completely [17-19]. Twelve patients developed GFV rebleeding over the 28 years of our work. Rebleeding usually occurred within 1 year following primary hemostasis and resulted primarily from incomplete GFV obliteration. Rebleeding was rare in localized-type GFV and, in post-mortem investigations after initial endoscopic ablation, histological examination showed that the vessel had been completely obliterated with fibrosis and lacked surrounding dilated vessels [19]. Nonetheless, in a few vascular type 2 GFVs, complete occlusion of all varicose veins could not be achieved. Numerous remaining inflow veins unable to be occluded with the Histoacryl® mixture developed new GFV lesions. EUS-CD is the most reliable method for checking for GFV [16-20]. Therefore, EUS-guided cyanoacrylate injection might be effective in treating any remaining GFV bleeding that standard endoscopy cannot detect.

For patients who respond poorly to Histoacryl® reinjection, non-endoscopic approaches, such as surgical intervention, transjugular intrahepatic portosystemic shunt, and balloon-occluded retrograde transvenous obliteration, seem to be safe and effective [4,5]. Kok et al. [26], suggested that an alternative combined approach is necessary for a GV larger than 10 mm in diameter. These approaches involve the application of a detachable snare or flow-reducing techniques in which a coil is used. Likewise, Romero-Castro et al. [27,28]. Suggested combining EUS-guided and flow-reducing techniques in which coils are placed under EUS guidance. These approaches are not considered the first choice in managing GFV bleeding, because they are complex and demand specially trained expert endoscopists [27-30].

This study showed that, apart from a few vascular Type 2 GFVs, endoscopic Histoacryl® injection with in-house technique stops GFV bleeding in the majority of cases. During the relatively long follow-up, the death rate due to GFV bleeding was 9% (6/68), the main cause being liver failure followed by hepatocellular carcinoma.

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These data are similar to those reported in this clinical setting [7,31-33]. In a previous study, [34] we first collected relevant baseline data of patients scheduled to undergo Histoacryl® injection for GFV bleeding. Univariate analyses of these data revealed that Child-Pugh class, hepatocellular carcinoma, and an association with minimal EV negatively affected a patient's survival time. In this study, bleeding from a minimal EV after GFV eradication became as severe as GFV rebleeding rates. Preventive endoscopic therapy that could be performed to treat EV carried the risk of the EV becoming uncontrollably severe.

Localized-type ("isolated") GFVs have been reported to poorly respond to endoscopic therapy because of high blood flow [1-5]. However, using endoscopic Histoacryl® injection, it was easy to obliterate localized-type GFVs consisting of a single varicose vessel without EV. Furthermore, the prognosis in this case was better than that for diffuse-type GFVs.

Our study has some limitations that should be taken into consideration. First, this study includes a retrospective cohort and the intervention was conducted in a single arm with no control group or other relevant modalities for comparison. Prospective trials with a randomized design are warranted to determine if our strategy is superior to other endoscopic injection techniques with respect to safety, treatment quality, and efficiency.

In conclusion, the use of Histoacryl® mixture for managing GFV bleeding is invasive, but this endoscopic procedure is gentle, simple, and does not require a high level of skill. It requires one skilled endoscopist who has experienced puncturing for the GFV and has a good understanding of the vascular anatomy of the GFV site and Histoacryl® polymerization. The results obtained over the course of 28 years of clinical practice support our conclusions that endoscopic Histoacryl® injection is an efficient strategy in the short and long term with a favorable safety profile. Our standardized endoscopic technique employing the injection of Histoacryl® mixture with 50% glucose was effective at minimizing the rate of life-threating GFV bleeding. We hope that the experiences outlined in this report help guide clinicians in managing GFV bleeding.

Acknowledgment

The authors did not request or receive any support from the manufacturers of Histoacryl® or Lipiodol.

Conflicts of interest and source of funding

All authors declare that there are no conflicts of interest related to this article and that this study did not receive external funding.

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