

Long-term follow-up of endoscopic Histoacryl glue injection for the management of gastric variceal bleeding

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Summary

Background: Variceal bleeding is an acute medical emergency with high mortality. Although less common than oesophageal variceal haemorrhage, gastric variceal bleeding is more severe and more difficult to control. The optimal therapy for gastric variceal bleeding remains unclear although endoscopic injection of *N*-Butyl-2-Cyanoacrylate (Histoacryl) glue is often used. However, its long-term efficacy is poorly described. We studied the immediate and long-term effects of Histoacryl glue injection as treatment for bleeding gastric varices in a large UK hospital.

Method: Endoscopy records and case notes were used to identify patients receiving Histoacryl injection for gastric variceal bleeding over a 4-year period.

Results: Thirty-one patients received Histoacryl for gastric variceal bleeding. Seventy-four per cent patients had alcohol-related liver disease and 61% of

cirrhotics were Childs Pugh grade B or C. Fifty-eight per cent were actively bleeding during the procedure with 100% haemostasis rates achieved. Two patients developed pyrexia within 24 h of injection settling with antibiotics. No other complications were encountered. Mean overall follow-up was 35 months, with mean follow-up of survivors 57 months. Forty-eight per cent patients had endoscopic ultrasound assessment of varices during follow-up with no effect on rebleeding rates. Thirteen per cent required subsequent transjugular intrahepatic portosystemic shunt placement. Gastric variceal rebleeding rate was 10% at 1 year and 16% in total. One- and two-year mortality was 23% and 35%, respectively.

Conclusion: Endoscopic injection of Histoacryl glue appears to be a safe and effective treatment for gastric variceal bleeding. Further data are required to compare it with other therapies in this situation.

Introduction

Variceal haemorrhage is a major cause of mortality and morbidity in patients with liver cirrhosis and portal hypertension.^{1–3} Varices form as a result of portal hypertension, which is due to both resistance to portal blood flow and increased portal venous blood inflow. Of those patients who develop liver cirrhosis, one-third will go on to have a variceal

bleed, which is predicted by variceal size, advanced liver disease and red wale marks on varices.^{4,5} Mortality from variceal bleeding remains high, with a 6-week mortality of at least 20%,^{7–9} which increases with severity of the liver disease.

Although, the most common site of variceal bleeding is oesophageal, gastric varices are present in 5–33% of patients with portal hypertension with incidence of bleeding ~25% at 2 years.^{10–12}



Figure 1. Gastric varices (Sarin IGV-1) seen on retroflexion of the endoscope in the stomach.

Gastric variceal bleeding is also more severe with higher rebleeding and mortality rates^{12–16} than that of oesophageal varices. Gastric varices (Figure 1) can occur alone or in combination with oesophageal varices and are often larger and located deeper in the submucosa than oesophageal varices.

Although endoscopic variceal band ligation (VBL) is well established as the treatment of choice for oesophageal variceal haemorrhage,^{1–3,17} it is less effective for gastric varices. Other endoscopic therapies for gastric variceal bleeding include injection therapy with standard sclerosants, Thombin or *N*-Butyl-Cyanoacrylate glue (Histoacryl). Radiological interventions include transjugular intrahepatic portosystemic shunt (TIPS) and less commonly balloon-occluded retrograde transvenous obliteration (BRTO). However, the availability of these radiological procedures in the UK often limits their use in the acute setting.

Following reports describing the efficacy of Histoacryl injection for gastric variceal bleeding, this treatment has been recommended in some guidelines as a first line therapy,^{2,9,18} however, there are limited data on long-term results. The aim of our study was to evaluate the immediate effects and long-term efficacy of Histoacryl injection for the treatment of bleeding gastric varices.

Methods

Detailed endoscopy records were used to identify patients who had received Histoacryl injection therapy over a 4-year period (January 2001–January

2005). The case notes were obtained and reviewed and data gathered. Information was recorded including laboratory parameters, aetiology of liver disease, the bleeding episode, endoscopic findings and therapy and endoscopic and hospital follow-up. General Practitioners were contacted if the patient had defaulted from hospital follow-up to clarify when the patient was last seen, whether the patient had a documented repeat gastrointestinal bleed and whether the patient was alive or deceased (along with details of any death). Follow-up was until 31st December 2008 or most recent clinical assessment.

All study patients were admitted with either haematemesis and/or melaena as their presenting complaint. Gastric variceal bleeding was confirmed in all patients at endoscopy by observation of either actively bleeding gastric varices, or recent stigmata of haemorrhage (cherry red spot, fibrinous clot) on gastric varices with no other source of bleeding identified. Initial endoscopy and Histoacryl injection was performed by a Consultant Gastroenterologist or Surgeon on the hospital emergency endoscopy rota.

During endoscopy with a standard forward viewing video endoscope, Histoacryl (TM, Braun, Melsungen, Germany) was injected using a standard protocol. Histoacryl was mixed with Lipiodol (Laboratoire Guerbet, Aulnay-Sois-Bois, France) in a 1:1.4 mixture (0.5 ml of Histoacryl with 0.7 ml Lipiodol). Lipiodol is an oily contrast agent used to delay glue polymerization and minimize risk of endoscope damage. After initial flushing of both the endoscopy channel and 21-gauge sclerotherapy needle with Lipiodol, one or two injections of Histoacryl and Lipiodol mixture were injected into the gastric varix. A 2 ml flush of saline via the sclerotherapy needle was used following injection of each aliquot of the mixture. Success or failure of initial haemostasis was assessed by the endoscopist's visualization of bleeding cessation. Any patient with concomitant oesophageal varices also underwent VBL after Histoacryl injection of the gastric varices. Pre-endoscopic prokinetic agents or gastric lavage and post-injection chest X-ray were not administered or arranged unless clinically indicated. All patients were given 7 days of Ciprofloxacin therapy as recommended by current guidelines.¹

Follow-up endoscopy was carried out after 2–4 weeks, unless clinically indicated earlier. Success of treatment on follow-up endoscopy was assessed either by direct visualization with careful probing with the blunt catheter (pre-August 2002), or by endoscopic ultrasound (EUS) after August 2002. The rationale for EUS in this setting was to assess the flow of blood with Doppler probe

measurements after the initial Histoacryl glue injection. If no flow was detected throughout the varix, then no further injection of glue was given. Portal pressure monitoring was not routinely performed. At follow-up endoscopy, further Histoacryl injection was given dependant on the endoscopist's assessment of the gastric varices. A rebleeding episode was defined as haematemesis or melaena along with endoscopic confirmation of gastric variceal bleeding or stigmata of recent haemorrhage.

This was an audit of management rather than research, with no extra investigations or procedures undertaken and no randomization or allocation to interventional groups. Therefore, ethical approval was not required or sought. Data were expressed as per cent, mean (\pm SD) or median (range) as appropriate. A significance value of <0.05 was chosen. Follow-up was assessed by Kaplan–Meier graphs and comparisons made using log-rank analysis.

Results

Patient characteristics

Thirty-one patients (25 male and 6 female) received endoscopic Histoacryl injection for gastric variceal bleeding over the study period. Patient characteristics are shown in Table 1. Twenty-three (74%)

Table 1 Patient characteristics (n=31)

Mean age (\pm SD)	54.0 (\pm 11.9)
Male:Female	25:6
Aetiology (n) (%)	
Alcohol	23 (74)
Hepatitis C	3 (10)
Hepatitis B	1 (3)
Cryptogenic cirrhosis	1 (3)
Nodular regenerative hyperplasia	2 (6)
Segmental thrombosis	1 (3)
Childs grade for cirrhotic patients (n=28) (%)	
A	11 (39)
B	12 (43)
C	5 (18)

patients had alcohol-related liver disease, 88% of whom had been drinking alcohol within 1 week of admission.

Classification of varices and therapy

The established Sarin classification for gastric varices is shown in Table 2 with the breakdown for our patients in Table 3. At the time of initial endoscopy, 21 (68%) patients had GOV types I or II. The median number of endoscopies per patient was two (range 1–5) and the median number of Histoacryl injections per session was two (range 2–5). Ten patients had pre-endoscopy intravenous terlipressin or octreotide with the remainder having it instituted during or after endoscopy. Two patients had a Sengstaken-Blackemore tube inserted prior to endoscopy and two patients were intubated at the time of initial endoscopy due to reduced levels of consciousness.

Endostasis

Of the 18 (58%) patients who were actively bleeding from their gastric varices at the index endoscopy, immediate endoscopic haemostasis was achieved in 100%. Those who were not actively bleeding at initial endoscopy all had stigmata of recent haemorrhage on their gastric varices and no bleeding was seen after Histoacryl injection.

Complications

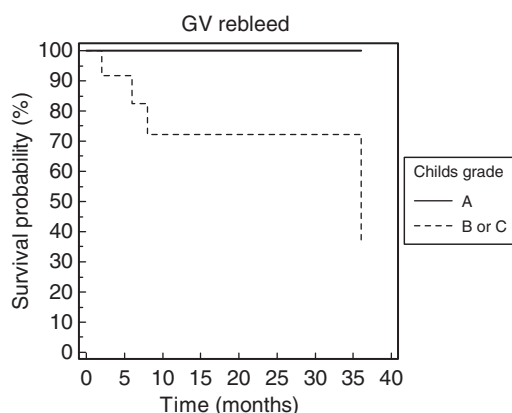
Two patients (6%) developed pyrexia within 48 h of Histoacryl injection. No bacteria were identified on routine cultures and in both patients the pyrexia settled with our routine policy of 7 days ciprofloxacin treatment. No other complications were identified and in particular there were no symptoms or signs of distant embolization. There was no damage noted in the endoscopic or clinical records to the endoscopes used in these procedures, and none were sent for repair in the week following the procedure.

Table 2 The Sarin classification of gastric varices

Gastro-oesophageal varices type 1 (GOV-1)
Gastric varices continuous with oesophageal varices extending <5 cm along the lesser curve of the stomach.
Gastro-oesophageal varices type 2 (GOV-2)
Gastric varices continuous with oesophageal varices extending towards the gastric fundus.
Isolated Gastric Varices type 1 (IGV-1)
Gastric varix found in isolation in the fundus alone.
Isolated Gastric Varices type 2 (IGV-2)
Gastric varix found in isolation outwith the fundus.

Table 3 Gastric varices at index endoscopy (*n*=31)

Active bleeding	18 (58%)
Recent stigmata of bleeding	13 (42%)
Sarin gastric variceal classification	
GOV-1	3 (10%)
GOV-2	18 (58%)
IGV-1	9 (29%)
IGV-2	1 (3%)

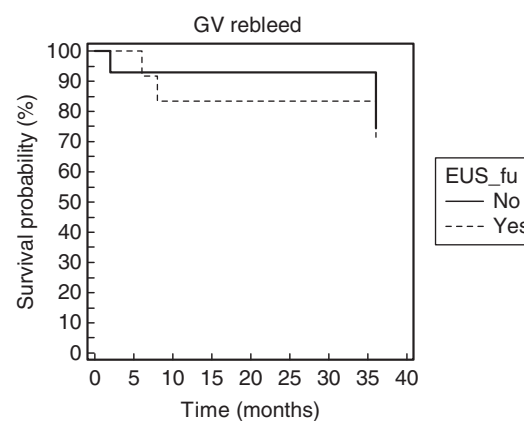
**Figure 2.** Kaplan–Meier graph of gastric variceal rebleeding on follow-up: Childs A vs. B/C patients (*P*=0.012).

Follow-up

Two in-patients self-discharged against medical advice during their initial admission. Both were offered an outpatient clinic appointment and repeat endoscopy, but failed to attend. Nine (29%) patients in total failed to attend a follow-up clinic or endoscopy. None of these patients were readmitted to our hospital with an endoscopically proven gastric variceal rebleed. Four patients were not given β -blocker therapy due to contraindications and 15 (48.4%) patients had EUS assessment during follow-up. The mean overall follow-up was 34.7 ± 23.7 months with mean follow-up for survivors was 57.4 ± 11.1 months.

Rebleeding/further therapy

Five patients (16%) had a gastric variceal rebleed during follow-up (two with Child Pugh grade B and three with Childs Pugh grade C disease; see Figure 2). No patient had a gastric variceal rebleed during their index admission, but three rebled within the first year and two rebled after 3 years. All rebleeding patients were treated with repeat Histoacryl injection. This controlled bleeding in three patients, but the other two required TIPS insertion to good effect. The mean time to TIPS

**Figure 3.** Kaplan–Meier graph of rebleeding dependent on EUS guided follow-up (*P*=0.747).

placement was $9.9 (\pm 2.0)$ months from initial bleeding episode. Due to small numbers, the outcome was not compared between gastric varices classification subgroups.

There was no significant difference in the rebleeding rate for patients undergoing EUS during follow-up compared with those who did not (Figure 3). No patient underwent BRTO, surgery or liver transplantation in the study period. During the follow-up period, three patients bled from oesophageal varices.

Mortality

A total of 19 patients died during follow-up. The 1-year and 2-year mortality was 23% and 35%, respectively. Sixty-three per cent of deaths were in patients with Childs B or C disease at the time of index bleed. One patient died of aspiration pneumonia 5 days after their index bleed (the only patient to die during their index admission). None died of gastric variceal bleeding although two died of oesophageal variceal bleeding during follow-up. Other recorded causes of death in those patients who died included: hepatocellular carcinoma (*n*=4), pneumonia (*n*=2) and spontaneous bacterial peritonitis (*n*=1), and two patients died peacefully at home. Cause of death was not recorded in seven patients; however from the hospital and GP records they did not present to hospital with, or die at home from gastrointestinal bleeding.

Discussion

Variceal bleeding remains a life-threatening emergency. Initial management centres on resuscitation, antibiotics and terlipressin therapy.^{1,3,9,18–20} Early endoscopy is required in those suspected of variceal haemorrhage to confirm the diagnosis and direct

therapy.^{1,2,18} While most published data relates to oesophageal variceal bleeding and confirms VBL as endoscopic treatment of choice in that situation, the optimum therapy for gastric variceal haemorrhage remains unclear. Therapeutic options can be divided into endoscopic and non-endoscopic (radiological or surgical) therapies. Gotlib and Zimmerman first applied endoscopic sclerotherapy in the treatment of a bleeding gastric varix in 1984.²¹ Although Sarin reported a 72% variceal obliteration rate in gastric variceal bleeds treated with ethanolamine sclerotherapy, significant complications and rebleeding rates of 50–90% have been reported using this technique.^{17,22,23}

There are limited data on the role of VBL in the management of gastric variceal bleeding. Although it can be useful for varices extending from the oesophagus along the proximal lesser curve (Sarin GOV-1), it is problematic for other types of gastric varices. More recently used injection therapies for gastric varices include thrombin and Histoacryl. There have been recent reports of thrombin injection for gastric variceal bleeding suggesting high-initial haemostasis rates,^{24–27} but there are no long-term data and no randomized studies comparing it with other treatments.

Endoscopic injection of Histoacryl has been recommended for gastric variceal bleeding.^{1,2,9,18} This long-chain Cyanoacrylate glue polymerises and solidifies within seconds following contact with aqueous media such as blood within a varix. This leads to obliteration of the varix from which the cast extrudes after 2–4 weeks. Mixing the Histoacryl with the oily agent Lipiodol delays polymerization.

Histoacryl injection has reported immediate haemostasis rates of 88–100%.^{28–32} We achieved immediate endoscopic haemostasis in 100% patients with Histoacryl injection, and our overall gastric variceal rebleeding rate was 16%. This rebleeding rate was similar to previously published studies including that by Seewald and colleagues who reported rebleeding in 17.1%.³³ Interestingly, in our study no Childs grade A patient rebled from gastric varices and no deaths were observed from gastric variceal rebleeding. Two other cohort studies reported rebleeding rates of 29–35% after initial haemostasis rates over 95%.^{34,35}

Rare complications of Histoacryl injection include cerebral or pulmonary embolism, splenic infarcts, mediastinitis, local abscess formation, detachment of the injection needle into the varix and endoscope damage. None of these complications occurred in our series. In addition, no complications were reported in Seewald's paper with a cohort of 131 patients receiving Histoacryl for gastric variceal bleeding.³³

In our centre, we have used EUS in our follow-up of gastric variceal bleeding since August 2002. The availability of this modality is limited out-with a teaching Hospital setting, but it may help identify flow in residual gastric varices requiring repeat injection therapy. Lee *et al.*³⁶ compared scheduled EUS-guided follow-up with 'on demand' follow-up after Histoacryl injection of gastric varices in a non-randomized study. They reported reduced late rebleeding in the EUS group. In our study, we found no significant difference in rebleeding whether EUS was used or not during follow-up. However, this finding should be interpreted with caution due to relatively small numbers in the EUS subgroup and larger studies are needed to clarify the role of EUS in this setting. Another limitation of our study is its retrospective design and the relatively high-default rate during follow-up (often seen in this patient cohort). However, in such cases we contacted the patients GPs to clarify outcome.

A recent study compared Histoacryl to propranolol for prevention of gastric variceal rebleeding.³⁷ The authors reported significantly reduced rebleeding and mortality with Histoacryl. To date, only two randomized studies have compared Histoacryl injection with other endoscopic modalities. Histoacryl had faster rates of variceal obliteration, improved control of acute bleeding and reduced need for rescue surgery compared with ethanol injection for fundal varices.³⁸ The other study concluded that gastric variceal obliteration with band ligation was more difficult and less effective than Histoacryl injection.³⁹

Interventional radiological procedures for the treatment of gastric varices include TIPS^{40–44} and BRTO.^{45–47} Both appear effective for bleeding control, but are relatively invasive and the expertise required is not universally available, particularly in the acute setting. Indeed BRTO is rarely used outside Japan. TIPS procedure involves the creation of a portosystemic shunt between the portal vein and hepatic vein to reduce portal pressure. Complications include increased encephalopathy. Due to the expertise and availability issues and its invasive nature, it is often used as a second line therapy for gastric variceal bleeding after failed endoscopic treatment. Only three patients in our study required TIPS for rebleeding during follow-up, which was successful in all cases. A recent small randomized trial from Taiwan was the first to compare TIPS with Histoacryl injection for gastric variceal bleeding.⁴⁸ Histoacryl was superior for variceal obliteration but led to a higher rebleeding rate. Larger trials are required to compare these treatment modalities.

In conclusion, our data suggest that endoscopic injection of Histoacryl is a safe and effective treatment for gastric variceal bleeding. Further randomized trials comparing Histoacryl, thrombin and TIPS will help to optimize future management of this challenging condition.

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Conflict of interest: None declared.

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