Endoscopic Cyanoacrylate Glue Injection in Management of Gastric Variceal Bleeding: US Tertiary Care Center Experience

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Background/Aims: Although endoscopic cyanoacrylate glue injection (ECGI) is recommended as first-line treatment for bleeding gastric varices (GV) there is still limited experience with this method in the US. Our aim was to analyze our 10-year experience of ECGI for treatment and prophylaxis of gastric variceal bleeding. **Methods:** Records of patients undergoing ECGI of GV at our US tertiary care center between 6/2005 and 5/2015 were reviewed. Assessed outcomes were primary hemostasis, early rebleeding during hospitalization, recurrent bleeding during follow-up, eradication and recurrence of GV. **Results:** Prophylactic ECGI was performed in 16 patients with large GV. Eradication was achieved in 15 (94%). During the median follow-up of 27 (IQR 7–47) months, 4 patients (26.6%) had variceal bleeding; all were treated successfully with ECGI. Fifty-seven patients underwent ECGI for GV bleeding. Primary hemostasis was achieved in all. Early rebleeding occurred in 2 (3.5%) and durable hemostasis could not be achieved. Follow-up beyond initial hospitalization was available in 41 patients. Bleeding recurred in 8 (19.5%) patients during a median follow-up of 12 (IQR, 3–51) months. Eradication of GV was achieved in 92% of patients but recurrent varices were found in 44% during a median follow up period of 33 months. **Conclusion:** ECGI is effective in achieving hemostasis of bleeding GV and their eradication. Recurrent bleeding and recurrence of varices after complete obliteration however are not infrequent and continued surveillance is advisable. (J CLIN EXP HEPATOL 2018;8:181–187)

BACKGROUND

Esophageal varices are more common than gastric varices (GV) but bleeding from gastric varices tends to be more severe and is associated with a high mortality.¹ There are well established and effective endoscopic treatment modalities to manage esophageal varices, but treatment of GV remains challenging. Endoscopic band ligation is the preferred method to treat esophageal varices but has been reported to achieve primary hemostasis in less than half of patients with GV, and re-bleeding rates are as high as 63% at 2 years.^{2,3} Similarly, conventional sclerotherapy has low efficacy in gastric varices. In contrast, endoscopic cyanoacrylate glue injection (ECGI) has been successfully used in the management of gastric variceal bleeding

outside of the US. It is superior to band ligation and has been recommended as first line treatment in gastric variceal bleeding.^{4,5} Cyanoacrylate is a monomer which rapidly polymerizes on contact with hydroxyl ions and forms a hard glue that obliterates the varix. There is still limited experience with this method in the US because it is not currently approved by the Food and Drug Administration for this indication, and concerns for complications including embolization remain.

Alternatives to endoscopic therapy include endovascular therapies, such as transjugular intrahepatic portosystemic shunt (TIPS) and balloon-occluded retrograde transvenous obliteration (BRTO).^{6,7} Both of these interventions have been shown to be effective in achieving primary hemostasis and decreasing re-bleeding rates but require careful patient selection. New or worsening portosystemic encephalopathy contributes significantly to the long-term morbidity of TIPS. Therefore, TIPS is typically recommended as second-line treatment at centers with experience in ECGI.⁸

Here we report our 10-year experience of ECGI treatment for gastric variceal bleeding and prophylaxis at a tertiary US center.

METHODS

Study Design and Setting

Retrospective chart review study was performed at a US tertiary care center. The study was approved by our

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Abbreviations: BRTO: balloon-occluded retrograde transvenous obliteration; CT: computed tomography; ECGI: endoscopic cyanoacrylate glue injection; GV: gastric varices; ICD-9CM: International Classification of Diseases, Ninth Revision, Clinical Modification; IQR: interquartile range; TIPS: transjugular intrahepatic portosystemic shunt; US: United States <https://doi.org/10.1016/j.jceh.2017.11.002>

institutional review board. ECGI for GV at our center was first performed in June 2005. Electronic medical records of all patients with a diagnosis of ICD-9CM code 456.8 between June 2005 and May 2015 were manually reviewed to identify patients who underwent ECGI of GV.

Procedural Details

ECGI was performed by three gastroenterologists. Indications included active or recent gastric variceal bleeding. In selective patients, ECGI was also performed for primary prevention of variceal bleeding from large GV. Standard gastroscopes (GIF-160, GIF-Q160, GIF-180, GIF-H180, GIF-H180J) or therapeutic gastroscopes (GIF-XTQ160, Olympus Cooperation of the America, Center Valley, PA) were used for the procedure. The therapeutic gastro-scope with 6 mm working channel (GIF-XTQ160) was preferred during the latter years of the study period. Patients with evidence of active or massive variceal bleed-ing were intubated for the procedure.

After identifying GV, Indermil[®] (n-Butyl 2-cyanoacrylate, Connexicon Medical, Dublin, Ireland) or Histoacryl[®] blue (n-Butyl-2-cyanoacrylate, B. Braun Medical Inc., Beth-lehem, PA) was drawn in 3 cc syringes, undiluted or mixed with lipiodol in 2:1 to 1:2 ratios. Dermabond[®] (2-Octyl 2-cyanoacrylate, Ethicon, Inc) was in used in some cases. The varix was then punctured with a 23 gauge injection needle (Variable Injection Needle, Cook-Medical Inc. Bloomington, IN). Intravariceal injection was confirmed by injecting sterile water with low resistance and absence of submuco-sal swelling. The glue mixture was then slowly injected, usually in 1–2 cc aliquots, followed by injection of 1.2 cc of sterile water (for Indermil, Histoactyl) or normal saline (for Dermabond) to flush the glue contained in the needle catheter into the varix. The needle was then withdrawn and flushed with sterile water to prevent needle occlusion. Particular attention was paid to not applying endoscope suction in order to prevent glue clogging of the suction channel. After allowing time for the glue to polymerize, the varix was probed with the tip of the needle catheter to assess firmness. Soft varices were considered patent and further glue and lipiodol aliquot was injected with the goal to obliterate all patent GV. All patients received 5 days of broad spectrum antibiotics. Patients who were admit-ted for acute variceal bleeding received continuous octreo-tide infusions for 72 h. Patients were scheduled for a follow-up endoscopy in 4–12 weeks to assess the degree of obliteration of varices, and additional glue injection was performed if patent varices were found.

Outcome

Assessed outcomes were primary hemostasis, early rebleeding, variceal bleeding during follow-up, eradication of GV, recurrence of GV and complications. Primary hemostasis was defined as complete cessation of bleeding

at the end of the procedure. Rebleeding was defined as drop in hemoglobin > 2 g/dL along with clinical signs of bleeding. Bleeding that occurred during the index hospi-talization was defined as early rebleeding. Bleeding that occurred after the index hospitalization was defined as delayed re-bleeding. The source of bleeding was deter-mined by endoscopy. GV were considered to represent the bleeding source if there were endoscopic features of bleeding from patent GV or in the absence of an alterna-tive bleeding source. Eradication of GV was defined as complete obliteration or absence of GV during follow-up endoscopy. Recurrence of GV was defined as patent GV on subsequent endoscopies after complete eradication had previously been confirmed. All complications attributed to ECGI were reviewed, including emboli or infection. If CT scans had been performed in any patients after ECGI, these were reviewed for glue emboli.

Statistical Analysis

Observations were reported as frequencies, and central tendencies were expressed as mean or median with stan-dard deviation and interquartile range (IQR), based on the distribution of the data. Categorical variables were reported as numbers and percent frequencies of occur-rence. Association between categorical and continuous independent variables and eradication and recurrence of GV were assessed using chi-square and *t*-test, respectively. The Kaplan–Meier method was used to estimate the recurrence of GV after eradication had been achieved.

RESULTS

Seventy-three patients underwent ECGI over a period of 10 years, 16 for primary prophylaxis and 57 to achieve hemostasis. Patient demographics and procedural details are described in [Table 1](#).

ECGI for Primary Prophylaxis

Prophylactic ECGI was performed in 16 patients with large GV. Ten patients (63%) were on non-selective beta-blockers. At least one surveillance endoscopy was done in all patients. Median follow up was 27 months (IQR, 7–47 months). Complete obliteration of GV was achieved in 15 patients (94%, see [Figure 1](#)). In one patient ECGI failed to achieve complete obliteration due to a large number of GV. GV in this patient were the result of alcoholic cir-rhosis and splenic vein thrombosis, and he was further treated with splenic artery embolization. Four patients (26.6%) had gastric variceal bleeding during follow-up. Hemostasis was achieved with repeat ECGI in all. One of these patients underwent elective TIPS and another had revision of an occluded TIPS. Both of these patients did not have any further bleeding during follow-up.

Table 1 Demographics of Patients Who Underwent Endoscopic Cyanoacrylate Glue Injection for Gastric Varices and Procedural Details.

Variable	Hemostasis	Prophylaxis
Number of patient who underwent ECGI	57	16
Age, mean (SD)	59 (13)	63 (11)
Gender, male	41 (72%)	12 (75%)
Cirrhosis	47 (82%)	14 (88%)
Etiology of cirrhosis		
Alcohol only	18 (38%)	3 (21%)
Chronic hepatitis C only	12 (26%)	4 (29%)
NASH only	8 (17%)	4 (29%)
Primary biliary cholangitis	1 (2%)	0
Multiple etiologies	8 (17%)	3 (21%)
Child class		
A	28 (60%)	9 (64%)
B	13 (28%)	4 (29%)
C	6 (13%)	1 (7%)
Splenic vein or portal vein thrombosis	10 (18%)	1 (6%)
Concomitant esophageal varices ^a	42 (74%)	13 (81%)
Isolated fundic varices ^b	14 (24%)	3 (19%)
Esophageal varices treated in the same session	21 (37%)	3 (19%)
Type of glue used		
2-Octyl-cyanoacrylate	6 (11%)	1 (6%)
n-Butyl-2-cyanoacrylate (undiluted)	17 (30%)	1 (6%)
n-Butyl-2-cyanoacrylate with ethiodized oil	33 (58%)	13 (82%)
Both 2-octyl and n-butyl-2-cyanoacrylate	1 (2%)	0 (0%)
n-Butyl-2-cyanoacrylate with coil	0	1 (6%)
Glue aliquot injected per session, ml, median (IQR)	3.5 (2.8–5.8)	3.3 (2.3–6.0)
Number of patient who underwent TIPS	4 (7%)	2 (13%)

SD: standard deviation, IQR: interquartile range, TIPS: transjugular intrahepatic portosystemic shunt.

^aCorresponds to GOV2 of the classification by Sarin et al.

^bCorresponds to IGV1 of the classification by Sarin et al.

Figure 1 Outcome and complications of prophylactic endoscopic cyanoacrylate glue injection for gastric varices.

ECGI for Hemostasis

Fifty-seven patients underwent ECGI for hemostasis in gastric variceal bleeding. It was the primary treatment in all but one patient who underwent ECGI for bleeding despite patent TIPS. Primary hemostasis was achieved in all (Figure 2). Early rebleeding from GV during hospitalization occurred in 2 patients (3.5%) and durable hemostasis could not be achieved. In one patient with concomitant esophageal varices, bleeding occurred from a banding ulcer after esophageal variceal ligation. This stopped without endoscopic intervention.

Delayed Recurrence of Gastric Variceal Bleeding

Follow-up beyond index hospitalization for gastric variceal bleeding was available in 41 patients. Median follow-up duration was 12 months (IQR 3–51 months). Recurrent gastric variceal bleeding occurred in 8 patients (19.5%, Figure 2). Repeat ECGI was successful in treating recurrent bleeding in 4 patients. Three needed additional

interventions (TIPS in 2 patients and splenic artery embolization in 1 patient), and one patient died from multi-organ failure despite achieving hemostasis with repeat ECGI. Another patient choose comfort care and no intervention was performed for recurrence of bleeding that was felt to be from gastric invasion of a widely metastasized neuroendocrine tumor.

Eradication of GV

Overall, nine patients underwent additional interventions after the ECGI. These consisted of TIPS ($n = 4$), splenic artery embolization ($n = 2$), splenectomy ($n = 1$), splenectomy and splenic artery embolization ($n = 1$) and liver transplantation ($n = 1$). After excluding these 9 patients, endoscopic follow-up was available in 51 out of the remaining 62 patients. Median endoscopic follow-up duration was 10 months (IQR 3–43 months). GV were eradicated in 47 of 51 patients (92%). This was achieved with a single ECGI session in 36, with 2 sessions in 7 and with more than 2 sessions in 4 patients. On univariate

Figure 2 Outcome and complications of endoscopic cyanoacrylate glue injection for gastric variceal bleeding.

Figure 3 Kaplan–Meier curve to estimate recurrence of gastric varices after eradication of gastric varices with ECGI alone. Median time to recurrence of gastric varices was 33 months.

analysis, the rate of gastric variceal eradication was not associated with patient age ($P = 0.770$), gender ($P = 0.775$), presence of concomitant esophageal varices ($P = 0.347$), child class ($P = 0.448$), etiology of cirrhosis ($P = 0.416$) or indication for ECGI (prophylactic versus hemostasis, $P = 0.909$). A non-significant trend toward higher eradication was noted in patients on non-selective beta-blockers (97% versus 83%, $P = 0.084$).

Recurrence of GV After Eradication

Of the 47 patients in whom GV were eradicated, endoscopic follow-up was available in 32 patients. Median follow-up duration was 9 months (IQR 0–39 months). Recurrent GV were encountered in 14 patients. Median time to recurrence was 33 months (Figure 3). On Cox proportional hazard model, age, gender, Child class of cirrhosis, etiology of cirrhosis, presence of esophageal varices or use of beta-blockers did not predict recurrence of GV.

Complications

There were no complications that led to permanent morbidity in any patients. Immediate complications of ECGI included ischemic stroke without residual deficit on follow up in 3 patients, asymptomatic portal vein cyanoacrylate emboli in two patients and asymptomatic pulmonary emboli in 5 patients. There were no septic complications.

DISCUSSION

Our 10-year experience in a tertiary care US hospital documents feasibility of ECGI with high rates of hemostasis and eradication of GV. In our study, hemostasis in acute gastric variceal bleeding was achieved in 96% patients. This is similar to data reported in the literature with hemostasis rates exceeding 90%.^{9,10} These results are encouraging and support ECGI as an alternative therapy

for gastric variceal bleeding to emergency TIPS. Primary hemostasis in gastric variceal bleeding is critical and all three modalities in current practice (ECGI, TIPS, BRTO) have comparable success rate in excess of 90%.^{6,11–15} However, emergent TIPS has been reported to carry significantly higher procedural mortality and morbidity than ECGI.^{11,14,16} Active variceal bleeding at the time of TIPS placement is an independent predictor of inpatient mortality irrespective of the severity of hepatic decompensation.¹⁷ A major advantage of ECGI is that it can be performed at the bedside in the intensive care unit during the index endoscopy whereas TIPS placement requires transportation of the patient to a radiology suite. Further, TIPS has significant long term morbidity.¹⁵

The natural history of GV is not well established, with significant variability noted across studies. The incidence of bleeding from GV appears to be lower than from esophageal varices.¹ The annual bleeding rate in GV which never bled before is reported to be as low as 4–5%,^{18,19} although in one study bleeding occurred in 53% of patients with untreated GV during a median follow-up of 26 months.²⁰ On the other hand, the reported mortality from gastric variceal bleeding is very high.¹ Hence forth, every effort should be made in preventing gastric variceal bleeding. ECGI has been noted to be superior to non-selective beta-blockers but inferior to TIPS in this respect.^{7,20} In our study, ECGI for primary prevention was performed in a limited number of patients. Eradication of GV was achieved in most of the patients but 26.6% patients had gastric variceal bleeding during a median follow-up of 27 months. This appears to be high and puts the efficacy of ECGI for primary prophylaxis into questions. On the other hand, ECGI for primary prevention was only performed in selected patient with high risk varices, and it is impossible to assess the exact impact of ECGI without an untreated control group or knowing the natural history in this patient population.

The rebleeding rate after initially successful hemostasis of bleeding GV was 19.5% over a median follow up of 12 months is similar to the previous reports.^{21–23} These results suggest that the bleeding risk remains fairly high if ECGI is used in isolation. In our series, 3 patients who underwent elective TIPS after ECGI for recurrent gastric variceal bleeding had no further recurrence. Thus, we suggest to consider elective TIPS after ECGI in selected patients. These include those with recurrent bleeding or incomplete variceal obliteration on surveillance endoscopies.

One of the challenges in the treatment of GV is that not all the varices are visible endoscopically. Deeper varices are often noted on computed tomography and endoscopic ultrasound.^{24,25} It is not clear whether obliteration of these deeper varices impacts clinically meaningful outcomes, although studies using endoscopic ultrasound guidance in ECGI have reported lower rates of rebleeding.²⁶ However EUS-guided ECGI requires additional

resources and expertise, and in the absence of randomized controlled studies, there remains debate whether the best choice for variceal obliteration is via endoscopic or endosonographic visualization.

Previously beta-blockers have shown a decrease in recurrence of bleeding in GV with or without ECGI.^{20,27,28} Henceforth, we consider beta-blockers for primary bleeding prophylaxis in patients with large GV and for secondary prophylaxis after successful ECGI. In the presence of a gastroduodenal shunt, BRTO of GV has been reported as a safe and effective treatment modality for hemostasis and has a low rebleeding rate.^{29,30} As BRTO does not create a hepatic bypass of portal venous return, it does not carry a risk of encephalopathy.²⁹ This makes BRTO an attractive alternative to TIPS patients with hepatic encephalopathy. Major challenges in the use of BRTO are a limited availability of local expertise, and unlike ECGI, it cannot be performed at bedside in the ICU.

Complications of ECGI, usually embolic events or infections, have been reported to occur in up to 10% of patients. These include massive pulmonary emboli, splenic infarction, stroke, liver emboli and mesenteric infarction.³¹ In our series the routine use of radiopaque ethiodized oil in most cases allowed identification of asymptomatic emboli that would not have otherwise been detected. However, CT scans were not routinely obtained. It must therefore be assumed that the observed rate of asymptomatic emboli and even of embolic events with minor symptoms is a gross underestimation. The use of endoscopic ultrasound guided coil-insertion combined with glue injection has been attempted by multiple investigators without a consistent decrease in embolic complications due to both glue and coil migration.^{32,33} The risk of embolization is likely influenced by the speed and volume of glue injection. We adopted a process of slow injection of small aliquots of glue over 20–30 s.

Bacterial translocation in the setting of acute variceal bleeding is a well-recognized phenomenon and septic complications have also been reported in elective ECGI.³⁴ Therefore, antibiotic prophylaxis is recommended. In our practice, all patients undergoing ECGI received broad spectrum antibiotics and septic complications were not encountered.

There are several limitations to this study. It is a single center, retrospective study with limited sample size, and no uniform follow-up and slight change of treatment protocols over time due to changes in glue availability. Further, routine imaging to assess for glue emboli was not systematically obtained. On the other hand, our series reflects the experience with ECGI in an unselected patient population as all patients that were treated with ECGI for GV were included. The longer follow-up of our series compared to other US-studies provides valuable additional information regarding long-term outcomes namely

a substantial risk of delayed bleeding and recurrence of GV after prior eradication.^{15,26,35}

CONCLUSION

ECGI is a very effective modality in achieving hemostasis in gastric variceal bleeding and in minimizing the need for emergent TIPS procedures. Eradication of GV is achieved in the majority of patients but recurrence GV within 3 years is common. Thus ongoing surveillance is recommended and additional treatment modalities should be considered in selected patients. Although glue emboli are occasionally found incidentally, symptomatic complications of ECGI as a result of glue emboli remain rare. Novel strategies of endoscopic GV treatment include EUS-guided application of coils alone or in combination with cyanoacrylate glue. However, current data are insufficient to directly compare long term efficacy and embolic risk reduction with these methods.

CONFLICTS OF INTEREST

The authors have none to declare.

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