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Original Article

Endoscopic treatment of acute gastric variceal bleeding in patients with cirrhosis using isoamyl-2-cyanoacrylate

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Abstract

Context
Gastric variceal (GV) bleeding is a serious complication in patients with cirrhosis, as it is usually severe with high rate of mortality and rebleeding.

Aim
The aim of this study was to evaluate the efficacy and safety of endoscopic therapy with isoamyl-2-cyanoacrylate (Amcrylate) in patients with cirrhosis with GV (gastroesophageal varices type 2 and isolated gastric varices type 1) bleeding.

Patients and methods
We prospectively studied 34 patients with cirrhosis with bleeding GV who were treated with intravariceal injection of isoamyl-2-cyanoacrylate (Amcrylate).

Statistical method
Data were expressed as the mean ± SD or as number (%) for numerical variables.

Results
After a mean dose of 1.86 ± 0.49 ml (range: 1–3 ml) of isoamyl-2-cyanoacrylate was injected in each patient, hemostasis was achieved initially in 100% of patients and complete obliteration of GV in 100% of patients. Treatment-related complications occurred in 26.5% of patients (9/34), but all complications were transient and mild. Complications included ulceration at site of injection (8.8%), fever (2.9%), abdominal pain (5.8%), chest pain (5.8%), and transient dysphagia (2.9%). Only one (2.9%) patient died closed to the cyanoacrylate treatment during hospitalization owing to hepatic encephalopathy and hepatorenal syndrome type I. During mean follow-up of 11.9 + 5.2 months (range: 2 weeks–21 months), rebleeding occurred in 8.8% of our patients.

Conclusion
This study has demonstrated the efficacy and safety of endoscopic treatment of bleeding GV using isoamyl-2-cyanoacrylate injection with initial hemostasis and complete obliteration of GV with no serious complications and low risk of rebleeding and bleeding-related death.

Keywords: Cyanoacrylates, endoscopic variceal obliteration, endoscopy, gastric varices, hemostasis, isoamyl-2-cyanoacrylate, liver cirrhosis

Introduction

Bleeding gastroesophageal varices is a major complication in patients with cirrhosis. Although varices occur in ~50% of patients with cirrhosis [1,2], gastric varices (GV) are less common than esophageal varices (EV), with a prevalence of ~20% [3].

Bleeding from GV is also less common than EV, as ~15–25% of GV bleed during the patient's lifetime [4,5]. However, GV bleeding tends to be more severe, requires more transfusions, has a higher mortality rate (45%) [6] and also has a high rebleeding rate of 34–89% [4].

The management of GV has not been well studied as that of EV, and both the evaluation and treatment of GV are still controversial [7].

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Cyanoacrylates are synthetic glues that rapidly polymerize and solidify within seconds on contact with water or blood [8]. Cyanoacrylate injection was originally reported with rapid control of bleeding GV by Soehendra *et al*. [9].

Now cyanoacrylates injection therapy is considered to be the first-line endoscopic intervention for bleeding GV and for the secondary prevention of GV bleeding [10,11] and has been suggested for the treatment of GV bleeding by American Society for Gastrointestinal Endoscopy (ASGE) guideline [12], Baveno Consensus [13], National Institute for Health and Care Excellence (NICE) guideline [14], as well as American Association for the Study of Liver Diseases (AASLD) practice guideline [15].

N-butyl-2-cyanoacrylate (Histoacryl) has been used extensively in endoscopic therapy of GV for the past 20 years. It is mixed with the oily agent lipiodol delaying polymerization.

Recently a new cyanoacrylate isoamyl-2-cyanoacrylate (Amcrylate) has become available. The Amcrylate was injected without mixing with any other substances [16].

Elwakil *et al*. [17] compared *N*-butyl-2-cyanoacrylate (Histoacryl) and isoamyl-2-cyanoacrylate (Amcrylate) and concluded that there was no significant difference in efficacy in the management of GV between them.

The aim of this study was to evaluate the efficacy and safety of endoscopic therapy with isoamyl-2-cyanoacrylate (Amcrylate) in patients with cirrhosis with GV [gastroesophageal varices type 2 (GEV2) and Isolated gastric varices type 1 (IGV1)] bleeding.

Patients and methods

From January 2017 until June 2018, all patients with cirrhosis with bleeding GV (GEV2 and IGV1) at the GIT Endoscopy Unit and the Internal Medicine Department at Mataria Teaching Hospital were included in the study.

All patients with upper gastrointestinal bleeding and features suggesting cirrhosis who presented to the Emergency Department of Mataria Teaching Hospital were resuscitated with fluids and packed red blood cells and admitted to hepatic care unit and underwent upper endoscopy as soon as possible.

Either active bleeding was directly observed during endoscopy or they have had bleed within the past 24 h.

Patients with bleeding EV, nonvariceal causes of upper gastrointestinal bleeding, and those with severe comorbidities were excluded. Patients with noncirrhotic portal hypertension were also excluded.

Management after initial resuscitation

All patients received sandostatin intravenously. After a bolus of 100 μg, a continuous infusion with 50 μg per hour was instilled for 5 days. All patients got 2 g ceftriaxone once a day for 5 days.

All of the included patients underwent the following:

(1) A complete clinical evaluation.
(2) Laboratory investigations: complete blood count, liver profile, and viral markers (hepatitis B surface antigen and hepatitis C virus antibody) using the enzyme-linked immunosorbent assay technique.
(3) Abdominal ultrasonography for liver and spleen size, portal vein diameter, and ascites.
(4) Child classification according to the modified Child–Pugh's criteria [18].
(5) Upper gastrointestinal endoscopy using the video-endoscope Pentax EG-3490K or Pentax EG-3890LK (Pentax, Tokyo, Japan).

The EVs were classified according to their size at the gastroesophageal junction into four grades according to Westaby *et al*. [19].

The GV were classified according to Sarin and Kumar [20]:

(1) GOV1: continuation of EV into the lesser curvature.
(2) GOV2: esophageal and fundal varices are present in continuity with the greater curvature.
(3) IGV1: fundal varices are present in the cardia in the absence of EV.
(4) IGV2: fundal varices present in the stomach outside of cardiofundal region or first part of duodenum.

Therapeutic interventions

The intravariceal injection technique was performed according to Soehendra *et al.* [21].

Patients with recently and actively bleeding GV were treated with isoamyl-2-cyanoacrylate (Amcrylate; Concord Drugs Ltd, Hyderabad, Telangana, India) injection. An endoscopic injector with a 21 G needle was used. Undiluted isoamyl-2-cyanoacrylate was injected slowly intravariceally into the GV [22]. Each varix was injected with 1–3 ml of glue depending on the size of the varix, after which 2 ml of normal saline was injected to deliver the entire glue from the injector into the varix. After the injection, the needle was immediately withdrawn from the varix, and 2 ml of normal saline was injected to flush the remaining glue from the injector to prevent its obstruction [23].

Obturation of GV was assessed by probing the injected varices with the injector for firmness. If the varices remained soft, the injection was repeated to achieve complete obliteration.

The patients were monitored for any complications like chest pain, shortness of breath, hypoxia, abdominal pain, fever, cough, and rebleeding.

After the initial control of bleeding, a repeat endoscopy was performed after 2–4 weeks for treating remaining GV or EV. Follow-up after obliteration was performed by gastroscopy every 3 months to monitor for variceal recurrence or on demand in case of bleeding. The patients were followed until September 2018.

Esophageal varices

In concomitant EV and GV, GVs were primarily treated and then coexisting EV were treated primarily with endoscopic

rubber band ligation in either the same session or during follow-up. GEV1 (gastric extension) were treated also by endoscopic rubber band ligation. This approach was shown to be equivalent to cyanoacrylate injections [24].

Definitions

Active GV bleeding was defined as spurting or oozing of blood from a GV. Evidence of recent GV bleeding was defined as the presence of a white nipple or red plugs.

The morphology of the GV was classified according to the system proposed by Hashizume *et al*. [25]: tortuous (F1), nodular (F2), or tumorous (F3).

Successful initial hemostasis was defined as cessation of bleeding with no recurrence for 2 days [26].

Rebleeding was defined as bleeding related to GV, a new onset of hematemesis, coffee grounds vomitus, hematochezia, or melena, with a pulse rate more than 100 beats/min and blood pressure less than 90 mmHg after a 24 h period of stable vital signs and normal hemoglobin concentration [11].

Bleeding-related death was defined as any death occurring within 6 weeks from a hospital admission for GV hemorrhage [27].

Informed consent was obtained from all of the included patients, and the study protocol was approved by the research ethical committee of GOTHI.

Results

A total of 34 patients were included in this study. The mean age of patients was 47.9 ± 7.9 years (range: 23–68 years). There were 24 (70.6%) males and 10 (29.4%) females. Thirty-three (97%) were antibody-positive for hepatitis C virus and one (3%) patient was positive for hepatitis B surface antigen. The patients' Child–Pugh classes were as follows: A, 11 (32.3%); B, 16 (47%); and C, seven (20.6%). Only one (2.9%) patient had concomitant hepatocellular carcinoma. Fourteen (41.1%) patients had a previous history of EV bleeding (Table 1).

During mean follow-up of 11.9 ± 5.2 months (range: 2 weeks–21 months), rebleeding occurred in 8.8% of our patients (3/34).

A total of 28 patients had concomitant EV (Table 2) and 14 had history of bleeding from EV. Overall, 19 patients had concomitant band ligation, where 12 of them as secondary prevention, and seven as primary prevention of variceal bleeding. Only three patients had concomitant band ligation and gastric varix glue injection on the same session, whereas the other 16 patients had band ligation during follow-up 2 weeks after GV injection.

Results of injection of isoamyl-2-cyanoacrylate

The overall success rate of initial hemostasis (no recurrent bleeding within 48 h) was 100% (34/34). A mean dose of 1.86 ± 0.49 (range: 1–3 ml) isoamyl-2-cyanoacrylate was injected in each patient (Table 3).

Table 1: Clinical characteristics of patients (*n*=34) with gastric varices

Characteristics	Value
Male/female	24/10
Age [mean±SD (range)] (years)	47.9±7.9 (32-68)
Etiology of cirrhosis (hepatitis C/hepatitis B)	33/1
Child-Pugh class (A/B/C)	11/16/7
Associated with hepatocellular carcinoma	1
Previous esophageal varices bleed [*n* (%)]	14 (41.1)
On β-blocker [*n* (%)]	14 (41.1)

Table 2: Endoscopic findings of enrolled patients

Characteristics	*n* (%)
Sarin classification of gastric varices	
Gastroesophageal varices type 2	30 (88.2)
Isolated gastric varices type 1	4 (11.7)
Form of gastric varices (F_1/F_2/F_3)	3 (8.8)/23 (67.6)/8 (23.5)
Presence of concomitant esophageal varices and its grade	28 (82.3)
I	7 (20.5)
II	3 (8.8)
III	13 (38.2)
IV	5 (14.7)
Previous eradication	3 (8.8)
Concomitant band ligation	19 (55.8)
Bleeding appearance	
Active spurting	9 (26.5)
Stigmata of recent hemorrhage	25 (73.5)

Table 3: Outcomes following isoamyl-2-cyanoacrylate therapy for bleeding gastric varices

Variables	*n* (%)
Immediate hemostasis of active bleeding	34/34 (100)
Dose of Amcrylate [mean (range)] (ml)	1.86±0.49 (1-3)
Obliteration of gastric varices	33/33 (100)
After one session	31/33 (93.9)
After two sessions	2/33 (6.1)
Rebleeding	3/34 (8.8)
Time to rebleeding	
After 4 days	1
After 8 months	1
After 12 months	1
Complications	
Ulceration at site of injection	3 (8.8)
Fever	1 (2.9)
Abdominal pain	2 (5.8)
Chest pain	2 (5.8)
Transient dysphagia	1 (2.9)

Treatment-related complications occurred in 26.5% of patients (9/34), but all complications were transient and mild [ulceration at site of injection (8.8%), fever (2.9%), abdominal pain (5.8%), chest pain (5.8%), transient dysphagia (2.9%)].

Thirty-three patients had at least one follow-up endoscopy (as one patient died before doing follow-up endoscopy). Follow-up endoscopy revealed complete obliteration of GV in 100% of patients. Of those, 31 (93.9%) patients had complete obliteration of GV as evidenced by no varices or only hardened varices visualized at endoscopy after one session, whereas two patients needed second session to complete obliteration.

Only one (2.9%) patient died closed to the cyanoacrylate treatment during hospitalization (bleeding-related death): a 47-year-old female patient with hepatitis C virus-related cirrhosis and Child–Pugh class C developed a hepatic encephalopathy and hepatorenal syndrome type I leading to death within 14 days.

Patients were followed up for 11.8 ± 5.1 months (range: 14 days–21 months).

During the follow-up, four (11.7%) patients died, where three (75%) died of hepatic failure and one (25%) patient owing to progression of hepatocellular carcinoma.

Discussion

Many treatment methods are used for the management of bleeding GV.

Interventional radiology methods, such as transjugular intrahepatic portosystemic shunt (TIPS) [28] and balloon-occluded retrograde transvenous obliteration [29] and surgical therapies such as surgical portosystemic shunt creation, have been used for the treatment of GV bleeding with variable success rates [30]. They are often effective in treating GV but are technically difficult, are more invasive, and have high complication rates, including serious complications such as hepatic encephalopathy, intra-abdominal hemorrhage and death [31–34].

Lo *et al*. [35] have compared glue injection with TIPS in the management of GV bleeding. Variceal obliteration was achieved in 51% of the glue injection group compared with 20% in the TIPS group. However, there was a higher rate of rebleeding in those who had glue injection (38%) compared with those treated with TIPS (11%) over a mean follow-up period of 33 months.

Endoscopic therapies for GV bleeding include traditional endoscopic therapies used for EV, such as band ligation and injection of sclerosing agent sclerotherapy, and other therapies specific for GV include variceal obturation with cyanoacrylate glue and thrombin injection.

Sclerotherapy and band ligation have also been trialed in bleeding GV with limited success with respect to hemostasis, rebleeding, and obliteration of GV [3,36–38].

Sarin *et al*. [3] compared cyanoacrylate with alcohol injection and found a higher rate of hemostasis (78 vs. 38%; $P < 0.05$) and variceal obliteration (100 vs. 44%; $P < 0.05$) in the gluing group.

Three studies have compared glue injection with GV band ligation in patients with acutely bleeding GV [11,37,39]. Lo *et al*. [37] found gluing to be more effective in achieving immediate hemostasis (87 vs. 45%; $P = 0.03$) and in preventing rebleeding (69 vs. 46%; $P = 0.005$). In addition, this group found that the number of blood transfusions required was significantly lower in patients managed using glue injection (2.3 vs. 4.2 U; $P < 0.01$). Tan *et al*. [11] reported no difference in controlling active bleeding in the two groups but a significantly lower rebleeding rate in the gluing group (22 vs. 44%; $P < 0.05$).

Qiao *et al*. [39] found that active bleeding control was achieved in 93.9% patients in the cyanoacrylate injection group, compared with 79.5% in the band ligation group ($P = 0.032$); cyanoacrylate injection was superior for reducing rebleeding and recurrence of GV to band ligation.

A number of small case series using thrombin or fibrin glue (a mixture of human fibrinogen, factor XIII, and human thrombin) for acute GV bleeding were reported [7,40–44]. The advantage of thrombin injection is the absence of postinjection ulcer at the puncture site [42]. Theoretically, the rebleeding rate should be lower in the absence of ulcer formation. In most studies, the initial hemostasis rate is more than 90%, the rebleeding rate is between 0 and 28%, and the mortality rate is from 0 to 50%. Although initial case series showed promising results of thrombin injection for GV bleeding, the current evidence is not sufficient to recommend thrombin as a standard treatment. Further randomized controlled trials comparing thrombin with cyanoacrylate are still needed.

So the preferred first-line treatment for acute GV bleeding is endoscopic obliteration with cyanoacrylate injection [7].

In this prospective observational study, we used a new cyanoacrylate isoamyl-2-cyanoacrylate (Amcrylate). The Amcrylate was injected without mixing with any other substances [17]. A previous study [18] confirmed that it had the same efficacy in management of GV as Histoacryl. Amcrylate is more easy to use because of its reduced viscosity and less adhesive problems compared with *N*-butyl-2-cyanoacrylate. Amcrylate is also significantly more cost-effective than is *N*-butyl-2-cyanoacrylate.

In our study, initial hemostasis was achieved in 100% of patient after mean dose of 1.86 ± 0.49 of isoamyl-2-cyanoacrylate was injected in each patient. which is consistent with the results reported by investigators such as Callwell *et al*. [45], Greenwald *et al*. [46], Dhiman *et al*. [47], and Seewald *et al*. [48]. In many other studies, the initial hemostasis was more than 90%, for example, Belletrutti *et al*. [49], (93.5%), Lo *et al*. [35] (93%), King *et al*. [50] (97.1%), and Akahoshi *et al*. [26] (96.2%).

Thirty-three patients had at least one follow-up endoscopy. Of those, 31 (93.9%) patients had complete obliteration of GV as evidenced by no varices or only hardened varices visualized at endoscopy after one session of glue injection, whereas two patients needed two session to complete obliteration.

Our results were consistent with other reports which reported obliteration of GV in 100% after cyanoacrylate injection [26,46] although other studies found lower rate of obliteration, such as 51% [35], 75% [50], 84% [49], and 93% [47].

During a mean follow-up period of 11.9 + 5.2 months (range: 2 weeks–21 months), rebleeding occurred in three (8.8%) of our patients. Our result was nearly the same as Cheng *et al*. [51], who studied 635 GV cases treated with endoscopic injection using butyl cyanoacrylate and followed the patients for 3–115 months and recorded recurrent bleeding in 8.0% of patients. Dhiman *et al*. [47] reported rebleeding in 10.3%, whereas Seewald *et al*. [48] reported that only 5.5% had rebleeding after 1 year. King *et al*. [50] reported 15.5% rebleeding rate whereas many studies reported rebleeding rate at ~21–25% [11,45,46,49,52].

Treatment-related complications occurred in 26.5% of our patients (9/34) but all complications were transient and mild, a result comparable to previous reports. Huang *et al.* [53] mentioned that mild complications, such as pyrexia (10–35%) and chest or abdominal pain (5–30%), have been reported after treatment of bleeding GV by cyanoacrylate.

Although rare, fatal complications like systemic and pulmonary embolization had been reported [11,37], such events are especially commoner in those with large gastrorenal shunts and hepatopulmonary syndrome, and caution is required with the use of glue in such patients [10]. In our study, there were no postglue serious complications.

In a large study of 635 patients, Cheng *et al*. [51] reported that embolic complications were observed in only 0.5%. The lack of such complications in our patients was likely owing to the relatively small number of patients. Other factor that may have been important is the routine use of low-volume glue injections because many have reported that serious complications may be related to the volume of glue used.

Conclusion

This study has demonstrated the efficacy and safety of endoscopic treatment of bleeding GV using isoamyl-2-cyanoacrylate injection. The ability to obtain initial hemostasis, no serious complications, and the low risk of rebleeding and bleeding-related death are all advantages of this therapy.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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