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# Acrylate glue injection for acutely bleeding oesophageal varices: A prospective cohort study

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ABSTRACT

*Background:* Acrylate glue injection is seldom performed in patients with bleeding oesophageal varices.
*Aim:* To assess efficacy and safety of acrylate glue injection in patients with bleeding oesophageal varices, as well as the impact of this technique on subsequent variceal ligation.
*Methods:* Prospective study on 133 consecutive cirrhotic patients treated by intravariceal injection of undiluted *N*-butyl-2-cyanoacrylate into the bleeding varix. Outcome measures were initial haemostasis, recurrent bleeding, complications and mortality at 6 weeks.
*Results:* 52 patients were actively bleeding at endoscopy and 81 showed stigmata of recent haemorrhage. Initial haemostasis was achieved in 49/52 active bleeders (94.2% [95% CI 85.1–98.5]). Overall, early recurrent bleeding occurred in 7 patients (5.2% [95% CI 2.3–10.1]). No major procedure-related complication was recorded. At 6 weeks, death occurred in 11 patients, with an overall bleeding-related mortality of 8.2% [95% CI 5.8–15.3]. Mortality was higher in active (15.4% [95% CI 6.9–28.1]) than non-active bleeders (3.7% [95% CI 0.8–10.4], OR 4.7 [95% CI 1.05–28.7], $p = 0.02$). Of those surviving the first bleeding episode, 112 patients subsequently underwent ligation. No technical difficulties were encountered in performing the banding procedure which was successfully completed in all cases.
*Conclusions:* Emergency injection of acrylate glue is safe and effective for the treatment of acute bleeding oesophageal varices and does not hamper subsequent variceal ligation.


## 1. Introduction

Variceal haemorrhage is one of the most serious complications of portal hypertension and cirrhosis and its management remains a clinical challenge. Although overall survival has improved in recent years, mortality is still around 20% at 6 weeks, and is closely related to failure to control initial bleeding or early re-bleeding [1–3]. According to published guidelines [4,5] and consensus recommendations [6], endoscopic therapy should be performed in any patient who presents with documented upper gastrointestinal haemorrhage and in whom oesophageal varices are the cause of bleeding. Band ligation is the recommended form of endotherapy for acute oesophageal variceal bleeding although sclerotherapy may be used in the acute setting if ligation is technically difficult [3,7].

The tissue glue *N*-butyl-2-cyanoacrylate is a watery solution, which polymerises and hardens within 20 s in a physiological milieu and instantaneously upon contact with blood [8]. This makes it ideal for obliterating vessels and controlling bleeding. Endoscopic obturation using cyanoacrylate for gastric variceal bleeding was first reported more than 20 years ago [9] and is now considered to be the therapeutic option of choice for the management acute gastric variceal bleeding [3,4,10]. Despite its efficacy, this type of endoscopic haemostasis is seldom performed for the control of acute bleeding from oesophageal varices. In Europe, undiluted cyanoacrylate has long been approved for endoscopic use.

Aim of the present study was to assess the efficacy and safety of intravariceal injection of acrylate glue to control bleeding in patients with bleeding oesophageal varices (BOV). Secondary objective of the study was to evaluate whether this endoscopic approach had any detrimental impact on subsequent variceal ligation.

## 2. Patients and methods

This is a prospective study carried out at two tertiary care, teaching hospitals. The study was approved by the institutional review boards of the participating centres. Informed consent was obtained from each patient included in the study, or from their

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relatives. All cirrhotic patients admitted to the emergency department for upper gastrointestinal bleeding were considered eligible for the study. Those endoscopically confirmed to have a haemorrhage from oesophageal varices (i.e. visualisation of active bleeding, either spurting or oozing, or presence of a fibrin plug onto the varix) were included.

Varices were classified into 3 sizes – small, medium or large – by a semiquantitative morphological assessment (with small varices defined as minimally elevated veins above the oesophageal mucosal surface, medium varices defined as tortuous veins occupying less than one-third of the oesophageal lumen, and large varices defined as those occupying more than one-third of the oesophageal lumen) [11]. For the purpose of the study also patients with haemorrhage originating from gastro-oesophageal or junctional varices were included. Classification of gastric varices into junctional or fundic was made according to Sarin [12].

Exclusion criteria were: absence of informed consent; bleeding from fundic gastric varices; non-variceal bleeding; hepatocellular carcinoma; bleeding from portal hypertensive gastropathy; previous endoscopic treatments for oesophageal or gastric varices.

The technique of acrylate glue injection is not different from that already described for the treatment of gastric variceal haemorrhage [8], except for the fact that we used undiluted *N*-butyl-2-cyanoacrylate (Glubran, GEM, Viareggio, Italy) and not a mixture of cyanoacrylate and lipiodol, an oily contrast agent to delay polymerisation. Briefly, acrylate glue is injected intravariceally using a standard 23-G needle injector (DVI-23-MH, Cook Medical Ltd, Cork, Ireland). To minimise the risk of embolisation, not more than 1 mL of glue was injected into the varix at a time. The glue is slowly injected into the bleeding point, followed immediately by 2–4 mL of distilled water to deliver the glue from the dead space of the catheter. The endoscopy assistant announces the end of this second injection, and the operator retracts the needle. As the varix is filled, the glue spills from the rupture site with formation of a hard plug obliterating the bleeding point. If the bleeding persisted over 60 s after the first injection, a second 1-mL was injected with the same modality. Over the next few weeks, the overlying mucosa sloughs off, and the glue is extruded from the varix. Following the extrusion of the glue, the injection site re-epithelialises with scar formation (Fig. 1 a–c).

### 2.1. Outcome measures

Outcome measures were: initial haemostasis, failure to control bleeding, recurrent bleeding, complications, and 6-week mortality. Also, data on transfusions requirements after injection therapy, as well as length of hospitalisations and the number of needed repeat hospitalisation in the observation period were recorded. In patients with actively bleeding, effective haemostasis was defined as the absence of further bleeding for at least 2 min of observation after adequate irrigation of the treated site.

Failure to control bleeding was defined as bleeding persisting over 60 s after the second injection of acrylate or bleeding recurrent within the 2 min of direct observation of the bleeding site following haemostasis, with need to change therapy (balloon tamponade with insertion of a Blakemore tube) or one of the following criteria, whichever occurred first: (a) fresh haematemesis <2 h after therapeutic endoscopy; (b) 3 g drop in haemoglobin (>9% drop in haematocrit) if no transfusion is administered; (c) transfusion of 2 units of blood or more (over and above the previous transfusions) required to increase the Hct to above 27% or Hb to above 9 g/dL; and (d) death [6].

Clinically significant early re-bleeding was defined as any new episode or haematemesis and/or melena within a time frame of 120 h with decrease in haemoglobin values of at least 2 g/dL or transfusion requirement of 2 units of blood or more within 24 h

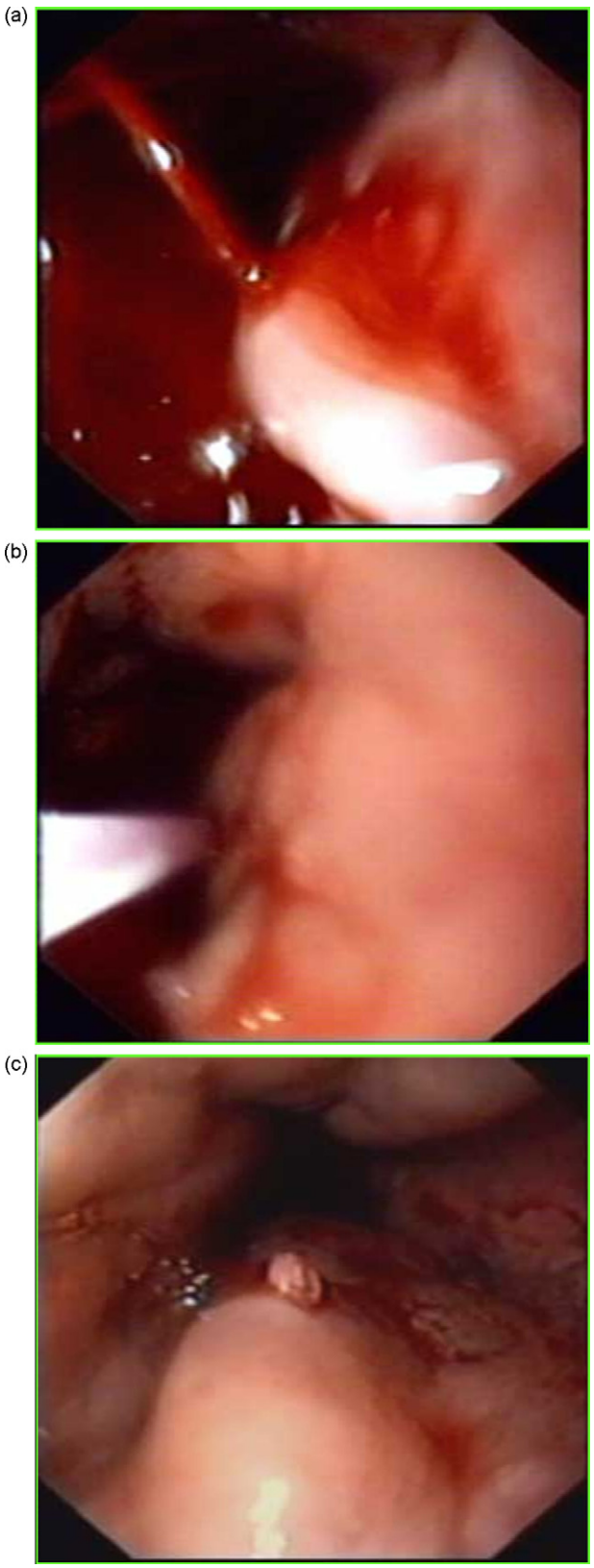



**Fig. 1.** Endoscopic picture of a spurting haemorrhage from a ruptured oesophageal varix (a); the glue is injected into the bleeding point with immediate arrest of bleeding (b); the varix is filled and the glue spills from the rupture site with formation of a hard plug still visible at 4 weeks (c).

of the time of admission, together with a systolic blood pressure <100 mmHg and/or pulse rate >100/min at time zero.

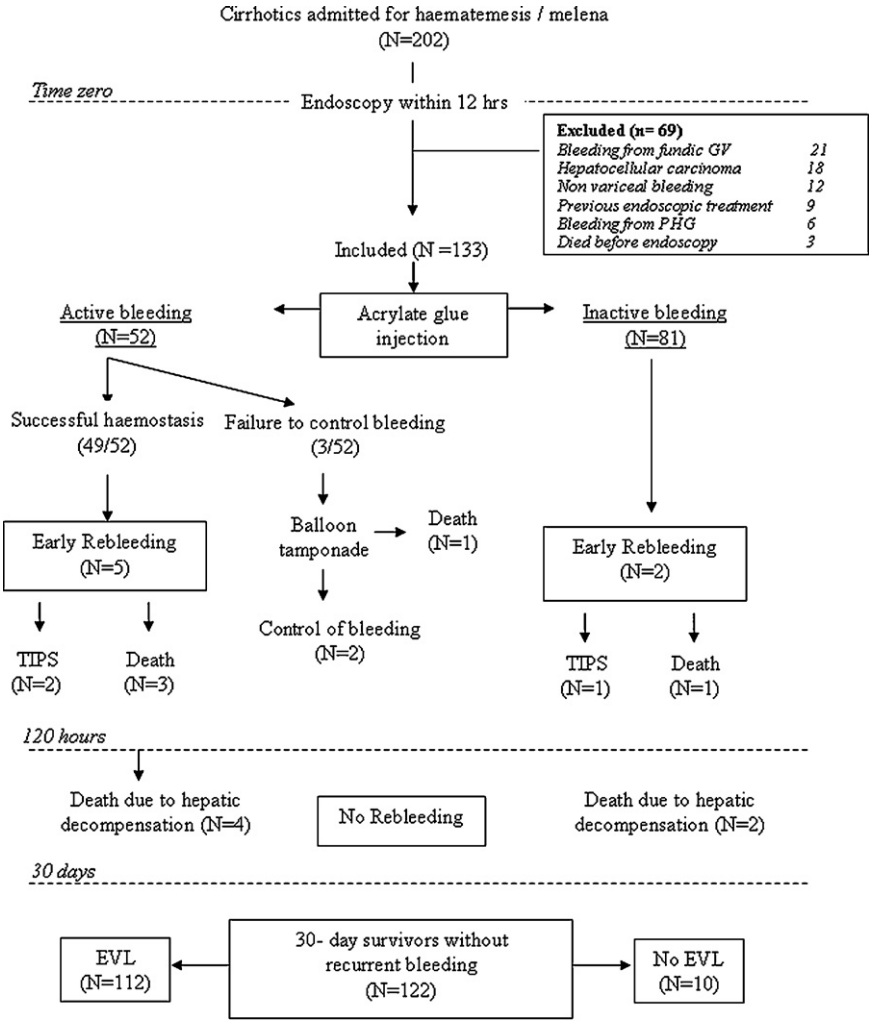
All patients received adequate fluid resuscitation and vasoactive drugs started immediately at the time of admission (somatostatin, i.v. bolus 250 (g + 250 (g/h infusion for 5 days), prophylactic antibiotics (norfloxacin or amoxicillin–clavulanic acid or i.v. ciprofloxacin), lactulose and/or enemas and blood transfusions to maintain the haematocrit at 24% to 30% [13,14].

Negative outcomes to the patient, equipment or personnel were systematically recorded on a purpose-built form duly filled by the operator or nurse on days 1, 7, 15, 30 and 45 through direct contact with the patient or referring physicians during the hospital stay and telephone contact after discharge. Involved physicians were alerted on the risk of distant embolisation of the tissue adhesive, which represents the only potentially life-threatening complication. All patients underwent close monitoring of respiratory function with continuous pulse oxymetry and arterial blood gases every 12 h within 48 h of the treatment and a chest X-ray the day after the procedure. In case of oxygen desaturation, chest pain or dyspnoea an echocardiography and an angio-CT scan were immediately performed.

Surviving patients were then scheduled for band ligation of varices as secondary prophylaxis 4 weeks after the index episode. In such a time frame all patients were given non-selective beta-blockers. Patients showing the persistence of the glue plug at endoscopy were postponed for a further period of 2 weeks. EVL sessions were repeated at 14-day intervals until variceal obliteration. Any technical difficulty in performing subsequent variceal ligation was recorded. Oral proton pump inhibitors with or without sucralfate were systematically given to patients after treatment until eradication. Once eradicated, EGD was repeated every 3–6 months to evaluate for variceal recurrence and need for repeat EVL.

### 2.2. Statistics

The statistical software packages S.P.S.S. for Windows, version 13.0 (S.P.S.S., Inc, Chicago, Ill) and STATA (StataCorp LP, College Station, TX) were used to analyse the data. Means ± standard deviation and ranges were used to summarise data for continuous variables, whereas percentages were used for categorical variables. The odds ratios with 95% confidence intervals were calculated and Chi-squared test or Fisher's exact test, when appropriate, was used. A $p$ value <5% was considered statistically significant. All data were analysed on an "intention to treat" basis.




*PHG: portal hypertensive gastropathy; EVL, endoscopic variceal ligation; TIPS, transjugular intrahepatic portosystemic shunt; GV: gastric varices*

**Fig. 2.** Study flow and outcomes recorded in the included population.

**Table 1**
Clinical and endoscopic features of treated patients ($n = 133$).

| | Active bleeding ($n = 52$) | Inactive bleeding ($n = 81$) |
|---|---|---|
| Males | 36 | 46 |
| Mean age (years) | 58 ± 19 | 61 ± 16 |
| Aetiology of liver cirrhosis | | |
| HBV/HCV hepatitis | 10/32 | 19/48 |
| Alcoholic | 10 | 14 |
| Child-Pugh's class (A/B/C) | 1/26/25 | 4/48/29 |
| Haemodynamic instability[a] | 16 (31%) | 9 (11.1%)* |
| Haemoglobin (g/dL) | 8.2 ± 1.9 | 9.3 ± (2.2)** |
| Oesophageal varices | 44 | 69 |
| Gastro-oesophageal (junctional) varices | 8 | 12 |
| Size of varices | | |
| Small (F1) | 1 | 2 |
| Medium/large (F2/F3) | 51 | 79 |

Values are expressed as means ± standard deviation.
[a] Systolic blood pressure <100 mmHg and heart rate >100 beats/min.
* $p < 0.01$.
** $p = 0.02$.

## 3. Results

Between January 2004 and December 2006, a total of 202 cirrhotic patients were admitted to the emergency departments of the two participating institutions for haematemesis and/or melena. Sixty-nine patients were excluded from the study for different reasons (Fig. 2). A total of 133 patients with endoscopically confirmed BOV were included, 52 (39%) with active bleeding and 81 (61%) with non-active bleeding at the time of endoscopy. Features of the study population are outlined in Table 1.

Endoscopic examination was performed as soon as the patient was haemodynamically stable, but always within 12 h of admission, with no difference in timing of endoscopy in the two groups of active or non-active bleeders (7.1 ± 3.6 h and 6.8 ± 4.1 h, respectively).

### 3.1. Active bleeders

In patients with active bleeding, initial haemostasis was achieved in 49/52 patients (94.2% [95% CI 85.1–98.5]). Control of haemorrhage necessitated a second 1-mL injection of cyanoacrylate in only 7 cases. In three patients the bleeding persisted (failure to control bleeding) and a Blakemore tube was inserted, achieving haemostasis in 2 of them. One patient died of uncontrolled bleeding. Recurrent bleeding occurred in 5/49 patients (10.2% [95% CI 3.8–21.2]). Of these, 2 underwent transjugular intrahepatic portosystemic shunt with control of re-bleeding and 3 died. Mortality of the acute phase (at 120 h) was 4/52 (7.7% [95% CI 2.5–17.5]).

### 3.2. Non-active bleeders

Recurrent haemorrhage occurred in 2/81 patients with non-active bleeding at endoscopy (2.4% [95% CI 0.4–7.9]. One patient underwent emergency TIPS and one succumbed to the bleeding episode.

Overall, early recurrent bleeding was recorded in 7 patients (5.2% [95% CI 2.3–10.1]), numerically more often in those with active bleeding at endoscopy than in those with non-active bleeding (10.2% vs. 2.4%, $p = 0.07$). Also the mortality of the acute phase was higher in active bleeders as compared to non-active bleeders (7.7% vs. 1.2%, $p = 0.07$).

No differences between the groups were noted in the number of transfusions required after injection therapy (3.6 ± 1.8 vs. 3.0 ± 2.2) or in length of hospitalisation (10.9 ± 9.2 vs. 11.3 ± 8.6, days, respectively).

No major procedure-related complication was observed, including damage to endoscopes or staff. Minor complaints were self-limiting abdominal discomfort or retrosternal pain (8 cases), mild pleural effusion (2 cases) and fever (1 case).

During the time frame between acrylate injection and band ligation, no patient experienced interval recurrent bleeding, but 6 patients died from progressive hepatic failure within 6 weeks of observation. Of these, 4 were actively bleeding at the time of endoscopy and 2 were not. Therefore, overall bleeding-related mortality was 8.2% [95% CI 5.8–15.3], with significant difference between active bleeders (15.4% [95% CI 6.9–28.1]) and non-active bleeders (3.7% [95% CI 0.8–10.4], OR 4.7 [95% CI 1.05–28.7], $p = 0.02$).

Out of 122 patients who survived the bleeding episode, 112 patients were subsequently submitted to EVL with eradication intent as secondary prophylaxis. Ten patients were not ligated for different reasons: lost to follow-up, i.e. patients did not show up at the first ligation appointment (7 cases); liver transplantation (1 patients), refused consent to EVL (3 patients).

In patients who underwent EVL protocol, mean number of banding sessions was 2 (range 1–4) and mean number of bands per session was 5 (range 3–7). Banding had to be delayed because the glue was still in place in 9 cases. No technical difficulties were encountered in performing the banding procedure which was successfully completed in all cases. Complications of EVL occurred in 8 patients (7.4%) and were all minor (3 transient dysphagia and 5 chest discomfort).

## 4. Discussion

In this large series of patients with acute bleeding from oesophageal varices, acrylate glue injection was both effective and safe, achieving high rates of initial haemostasis in active bleeders. Early recurrent bleeding occurred in 5.2% and overall bleeding-related mortality was relatively low (8.2% at 6 weeks). These figures compare favourably with the few available studies about acrylate glue injection in patients with BOV, most data being derived from small randomised-controlled trials or subgroups of patients with otherwise uncontrollable bleeding [15,16]. In a report on 44 patients endoscopically treated with cyanoacrylate and polidochanol, haemostasis was achieved in all cases and only minor complications were recorded [17]. Another study from Hong-Kong randomised 50 patients with inoperable hepatocellular carcinoma and acute BOV to either sclerotherapy or acrylate glue injection. There were no differences in failure to control bleeding, death, recurrent bleeding and cumulative survival [18]. A small randomised study on 36 cirrhotic patients reported significantly improved outcomes in the cyanoacrylate injection group as compared to conventional sclerosis group, with an absolute reduction in the in-hospital mortality rate of 39% [19].

Variceal ligation has been reported to be equally effective in both active and inactive variceal bleeding, though the rates of recurrent bleeding and mortality at 30 days were significantly higher among patients with active bleeding at endoscopy [20]. Our data confirm such findings: acrylate glue injection was effective in both active and non-active bleeders, and there was a clinically relevant higher risk of recurrent bleeding (not reaching significance likely due to a beta error) and bleeding related mortality in active bleeders.

Quite surprisingly, no recurrent bleeding was recorded in the time frame between acrylate injection and first session of banding. This may be partly due to secondary prophylaxis with beta-blockers, which were started as soon as oral re-feeding was allowed. For those seven patients that were lost to follow-up, we were unable to obtain information about further bleeding episodes or death, despite attempts to contact or their families or the referring physicians.

In our opinion, although technically more demanding than EVL, use of tissue adhesive retains all the advantages of injection therapies for variceal bleeding: it can be readily performed at the time of endoscopic identification of the source of bleeding without the need to take out the scope and load the ligating device; this saves time in situations were time is precious. Moreover, field of view is not limited, unlike emergency ligation where the hood with preloaded bands can limit endoscopic vision.

Reasons for reluctance to perform polymer injection in BOV is not known. It may be because alternative therapeutic options are available and band ligation – especially for initial bleeds – works well. This may not be the case for gastric variceal bleeding, a situation where both ligation and sclerotherapy can be either impracticable or poorly effective, and therefore tissue adhesive is seen as the only viable therapeutic option.

In our prospective study, acrylate glue injection proved both safe and easy to perform. Complications reported with this technique include distant embolisation, visceral fistula, septic complications, pericarditis, and also instrument-related problems [21–27]. The most serious risk from intravariceal glue injection is systemic embolisation. Fortunately, this is an uncommon adverse effect and was not observed in any patient in the present series. Technical factors that increase the embolisation risk are excessive dilution, rapid polymerisation, large volumes (>1 mL/injection), and rapid injection of the glue [28]. Glubran is used undiluted, polymerises a little more slowly than Hystoacryl and does not need to be mixed with lipiodol to delay polymerisation. Since most of the risks associated with cyanoacrylate are preventable, adherence to a standardised injection technique may help in minimizing the risk of potential complications and improve the long-term outcome.

If the glue sticks to the lens, the endoscope should be withdrawn and cleaned with ethanol or nail polish remover immediately. We have never experienced damage to the endoscope when using the glue. The endoscopy assistant should be well trained in the injection technique; a second nurse is required for preparing the additional injection catheters and cyanoacrylate vials. Care must be taken to protect the eyes of the patient and the clinical personnel. Goggles are required for eye protection during preparation and injection of the glue.

The main limitation to the present study is that it is not randomised, so that further studies on the outcomes of glue injection versus ligation would be required. Nonetheless, this study was not intended nor designed to prove any superiority of acrylate glue injection over standard forms of endoscopic haemostasis in the emergency setting, particularly band ligation. Second, because at present cyanoacrylate-based agents are not approved for endoscopic use by the Food and Drug Administration, the results of the study have a somewhat limited generalisability in the U.S. Finally, the study was not designed to investigate any economic outcome, since it was felt to be less relevant in the setting of a life-threatening condition such as acute variceal bleeding. Starting with banding at the time of the bleeding episode may entail a lower number of endoscopic sessions to eradicate varices. The two-step approach (first inject and then ligate) adds up the incremental costs of a needle injector and a vial of acrylate glue (indeed both inexpensive) to the costs of ligator device(s) in case of survivors. The higher number of endoscopic sessions required should intuitively be calculated as additional costs, although all fully covered by the National Health System with no economic burden to patients or third-party payers. In case of "interval" re-bleeding between glue injection and the first session of variceal ligation, costs would have raised significantly, but this event never occurred in our experience.

Variceal ligation is considered the treatment of choice for the prevention of recurrent variceal bleeding [4,6,29,30]. In our experience following acrylate injection to arrest bleeding, subsequent variceal ligation could be safely and effectively performed in over ninety percent of cases with eradication intent. No technical difficulties were reported in performing the procedure neither any adverse event related to the previous use of cyanoacrylate was recorded.

In conclusion, emergency injection of acrylate glue is safe and effective for the treatment of acute BOV and does not hamper subsequent variceal ligation. Future comparative trials versus band ligation are required; nonetheless endoscopists might consider this technique among the possible alternatives in the treatment of acute oesophageal variceal bleeding.

## Conflict of interest

None declared.

### List of abbreviations

BOV, bleeding oesophageal varices; EGD, esophago-gastro-duodenoscopy; EVL, endoscopic variceal ligation; PHG, portal hypertensive gastropathy; GV, gastric varices; TIPS, transjugular intrahepatic portosystemic shunt.

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