## REVIEW

# Management of fundic varices. Endoscopic aspects

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## BACKGROUND

Gastric varices (GV) are less prevalent than esophageal ones. It has been estimated that GV are present in 8-15% of patients with cirrhosis and portal hypertension. However, the prevalence of GV, in those patients with non-cirrhotic portal hypertension, has been estimated to be around 20%. GV should also be investigated in patients who present with splenic vein thrombosis (segmentary portal hypertension) (1-3). Although gastrointestinal bleeding from GV is less frequent than from esophageal varices, bleeding from GV is usually more severe (increased rate of morbidity, mortality, rebleeding and transfusion requirements) (1,4,5).

## GASTRIC VARICES CLASSIFICATION

Sarin´s classification divides GV according to their location in the stomach, as gastroesophageal varices (GOV) and isolated gastric varices (IGV) (Figs. 1 and 2). This classification is the most frequently used in clinical practice, as it correlates each type of varices with a specific risk of bleeding, modality of treatment, and vascular anatomy (4,5).

GOV are divided into 2 subtypes. GOV1 are gastric varices arising from the lesser curvature of the stomach and extending above the gastroesophageal junction as esophageal varices. GOV2 varices are located in the gastric fundus and extend towards the esophagus as esophageal varices. Both of them, GOV1 and GOV2, arise from the left gastric vein. GOV1 drain into the azygos vein and superior vena cava through the esophageal and paraesophageal veins. GOV2 follow the same route as GOV1 varices, but they also drain to the inferior vena cava vein through the subdiafragmatic left vein. GOV1

are the most common type of GV (70% of the total), but have a lower risk of bleeding (responsible for only 20% of GV bleedings). On the other hand, GOV2 represent only the 21% of all GV. IGV are even less common, and can be located in fundus (IGV1) (7%) or in the body or antrum of the stomach (IGV2) (2%), with no extension into the esophagus (4). IGV arise from the short gastric veins and the posterior gastric vein (both of them, collaterals from splenic vein), and may drain through the left subdiafragmatic vein, laterally to the inferior vena cava (gastro-cava shunt) or drain down to the left renal vein (gastro-renal shunt) (5). Figure 3 shows the vascular anatomy of gastric varices.

GOV2 and IGV1, but not IGV2, are both located in the gastric fundus, and therefore are named as fundic varices. Eighty-five per cent of patients who present with fundic varices will have a gastro-renal shunt (from the fundus to the left renal vein), which may be responsible for many physiological and therapeutic aspects of fundic varices (6-8).

Vascular anatomy and management of GOV1 and esophageal varices, as well as treatment response is similar, and therefore will not be discussed in this review. Although only 30% of all GV are located in the gastric fundus, they are responsible for nearly 70% of all GV bleeding (4). This review will focus on fundic varices management.

## TREATMENT OF BLEEDING FROM FUNDIC VARICES

### Primary prophylaxis

Risk factors associated with bleeding from fundic varices were analyzed by Kim et al. (9). Authors observed
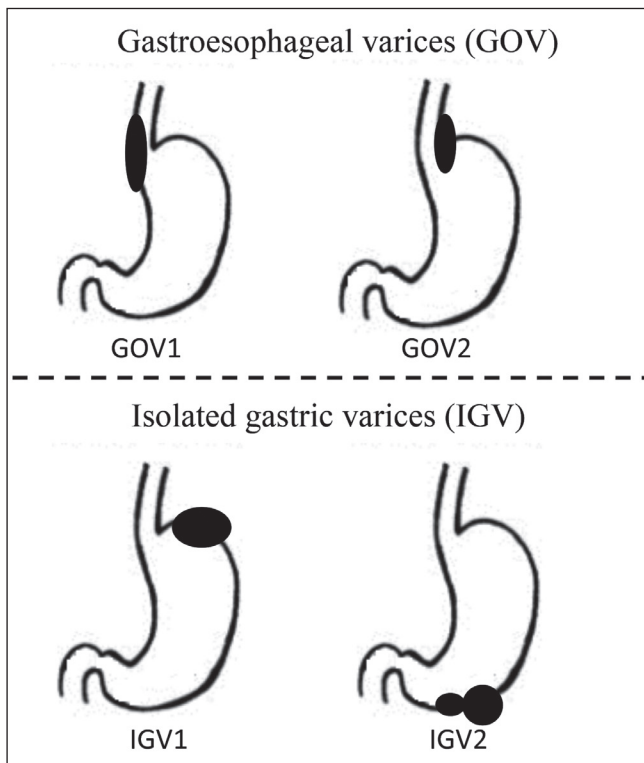
Fig. 1. Sarin´s classification of gastric varices.



Fig. 2. Examples of different types of gastric varices.
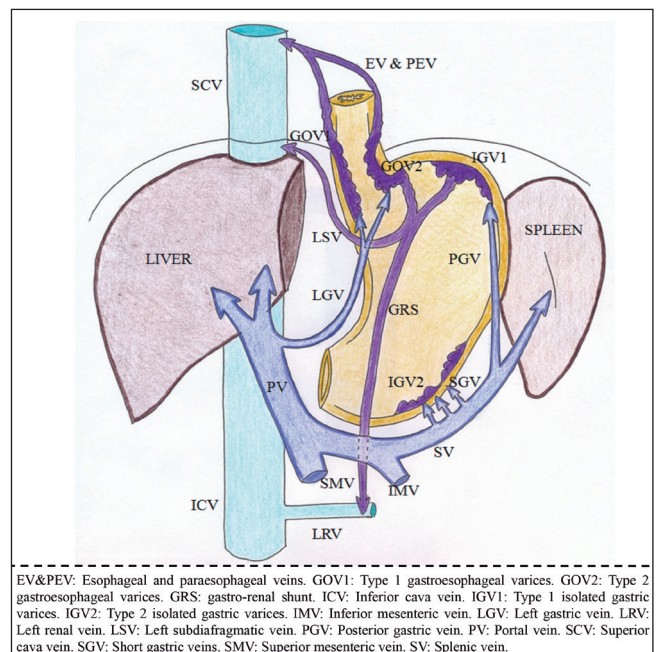


Fig. 3. Vascular anatomy of gastric varices: Origin and drainage.

that the degree of liver function (as measured by the Child-Pugh and/or MELD score), the size of the varix and the presence of red spots on its surface were all associated with the risk of bleeding (9). The international consensus on portal hypertension management held in 2010 (Baveno V) recommends the usage of non-selective beta blockers for primary prophylaxis in patients with GV (10). However, in 2011 Sarin et al. (11) conducted a randomized trial comparing three different strategies of GV therapy (cyanoacrylate injection *vs.* non-selective beta blockers *vs.* no treatment). Significant differences were observed favouring the use of cyanocrylate (CA) injection, in terms of prevention of bleeding and survival, when compared with no treatment. However, when compared with propranolol, CA only showed significant benefits in preventing the first bleeding. This study has been criticized due to important limitations, as highlighted by Tripathi (12): a) Alcohol was the only known etiology (nearly 50% of patients), with the remaining patients being classified as idiopathic (26%) or unknown (26%); b) most of the patients included in the study had GOV2 varices with a very small number of IGV1 cases; and c) results of the hepatic venous pressure gradient were heterogeneous, with a wide range of measures and some cases having less than 10 mmHg of gradient. The last international consensus on portal hypertension management held in 2015 (Baveno VI) (13), advocates that further studies are needed to evaluate the risk/benefit ratio of using CA in this setting before a recommendation can be made.
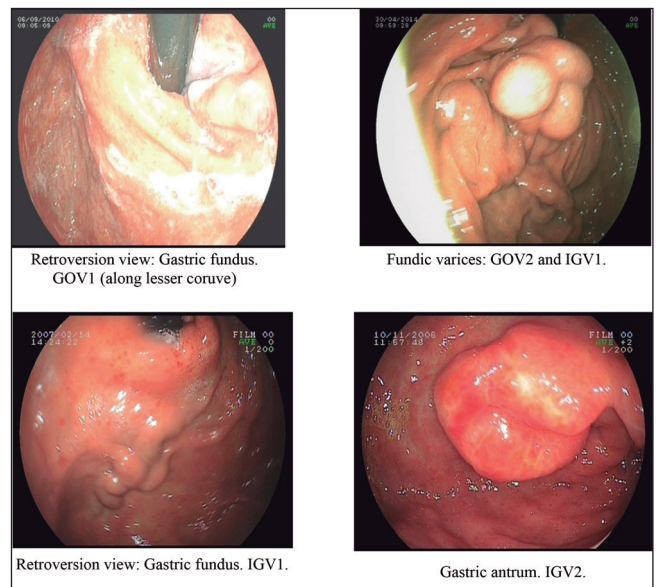
Due to these study limitations and the little scientific evidence for primary prophylaxis of GV, the Spanish consensus document, sponsored by the Spanish Association for the Study of the Liver (AEEH), recommend the use of beta-blockers (5;D), and to avoid CA injection for primary prophylaxis (3). However the previously cited study by Sharin et al. (11) may be taken into account in the next AEEH recommendations.

**Treatment of acute bleeding from fundic varices**

There is no strong evidence regarding which therapy should be performed in patients with an episode of acute bleeding from fundic varices. The initial approach for these patients is, as in esophageal varices bleeding (1,6,10,14), to initiate therapies directed to obtain patient hemodynamic stability, administer vasoactive drugs (somatostatin, terlipressin) and antibiotics, and transfuse blood as required (following a restrictive policy).

If endoscopic therapy is advised, we should know that there are three alternatives for such a treatment: CA injection, endoscopic band ligation and ethanol injection. The scientific evidence supporting the use of endoscopic therapy to treat these patients is limited, as most studies published include not only fundic varices and this may certainly limit the validity of conclusions obtained. Careful review of studies published on the literature, shows that the best endoscopic option for treating fundic varices that are actively bleeding is CA injection (Table I), with a reported technical success of approximately 90% (5,15-24). Endoscopic

band ligation may also be consider as an alternative, but should only be applied in selected cases of actively bleeding GOV2 of small size, and when the endoscopist has low experience with CA injection. In some studies endoscopic band ligation has been shown to achieve an elevated rate of hemostasis, similar to CA injection, but the elevated rate of rebleeding (close to 50% in some publications) does not allow us to recommend it as a first line therapy (23,24). Ethanol injection of bleeding gastric varices has also been reported, but existing evidence does not support its use, as it shows a lower efficacy and a higher complication rate than other endoscopic alternatives (21,22).

In those cases of active, massive, uncontrollable bleeding, balloon tamponade with the Sengstaken or Linton balloon appears to be the best therapeutic option. The efficacy and safety of both types of balloon in this setting has only been compared in a single study. It does appear that the Linton balloon, that is provided with a larger gastric balloon (600 ml of volume) than the Sengstaken balloon (400 ml), is probably more effective to obtain adequate mechanic compression of the fundic varices (25). Balloons

**Table I. Endoscopic treatments in acute fundic varices bleeding**

| Author, year (ref.) | Design/treatment | n; Follow-up (m) | Type of varix | Active bleeding (%) | Initial hemostasis (%) | Rebleeding (%) | Mortality (%) |
|---|---|---|---|---|---|---|---|
| Kind, 00 (15) | Obs (glue*) | 174; 36 | GOV1 (38%) GOV2 (45%) IGV1 (12%) IGV2 (5%) | 100 | 97 | 15.5 | 19.5 |
| Huang, 00 (16) | Obs (glue*) | 90; NA | IGV1 & GOV2 (94%) | 5.5 | 94 | 23 | 38.9 |
| Cheng, 07 (17) | Obs (glue*) | 146; 36 | NA | NA | 95 | 8 | 10 |
| Mumtaz, 07 (18) | Obs (glue*) | 50; NA | IGV1 (44%) GOV1 (32%) GOV2 (30%) | 22,7 | 100 | 14 | 6 |
| Marques, 08 (19) | Obs (glue*) | 48; 18 | GOV1 (35%) GOV2 (62%) IGV1 (2%) | 27 | 92 | 20.5 | 44 |
| Paik, 08 (20) | Obs (glue*) | 121; 1 | NA | 26 | 91 | 13 | 11.6 |
| Oho, 95 (21) | RCT (sclerosis^/glue*) | 24/29; 14 | GOV2 (45%) IGV1 (55%) | 100 | 67/93 | 30/25 | 67/38 |
| Sarin, 02 (22) | RCT (sclerosis^/glue*) | 17/20; 15 | IGV1 (76%) GOV2 (24%) | 46 | 62/89 | 25/22 | 19/10 |
| Lo, 01 (23) | RCT (band ligation/glue*) | 29/31; 9/14 | GOV1 (68%) GOV2 (24%) IGV1 (8%) | 43 | 45/87 | 54/31 | 48/29 |
| Tan, 06 (24) | RCT (band ligation/glue*) | 48/49; 23/20 | GOV1 (54%) GOV2 (26%) IGV1 (20%) | 31/31 | 93/93 | 44/22.5 | 69/55 |

Published studies on endoscopic treatments with N-butyl-2-cyanoacrylate in acute fundic variceal bleeding. m: Months; n: Number of patients; NA: Not available; Obs: Observational study; RCT: Randomized controlled trial; Ref.: Reference. *N-butyl-2-cyanoacrylate (bucrylate) was the type of glue used. ^Sclerosis was performed with ethanol injection.

have been shown to be very effective to achieve initial haemostasis (80%), but tend to rebleed after deflation (> 50%), and therefore should only be considered as a temporal bridge (24-48 h) to definitive therapy. After deflating the balloon, one of the following therapeutic options should be performed to prevent bleeding: CA injection, transjugular intrahepatic portosystemic shunt (TIPS), balloon-occluded retrograde transvenous obliteration (BRTO), or surgery for selected cases (1,2,6). Surgical aspects are beyond the focus of this revision (endoscopic therapy of gastric varices), and will not be discussed in this manuscript.

Placement of a TIPS has been shown to be very effective at controlling the episode of active bleeding, achieving an hemostasic rate as high as 90-100%, with a moderate risk of rebleeding (16-41%) (26-29) (Table II). Generally speaking, the TIPS should be considered if the bleeding is not controlled after CA injection, or at the time of balloon deflation (27,30). Treatment of collateral veins visualized by portography during the TIPS placement is not routinely performed; however, it has been recommended in the following situations: a) Venous collaterals seen on portography after TIPS placement; b) rebleeding from fundic varices after successful TIPS insertion; and c) venous gradient > 12 mmHg after TIPS placement (3,31,32). Contraindications for TIPS should be carefully studied in a case by case scenario, considering the patient clinical status (degree of liver dysfunction and portal hypertension: Bilirubin, albumin, platelets, sodium, past history of encephalopathy) and technical aspects like vessel permeability (29).

BRTO is a novel technique developed in Japan and performed in a few centers in the USA. It does appear to have a high technical success and efficacy (75-100%), with a low rebleeding rate (0-15%) (33). From a technical point of view, it should be acknowledged that a wide gastro-renal shunt is required to be able to reach the fundic varices from left renal vein, inflate the balloon inside the shunt, and finally inject CA to occlude the gastric varices (Fig. 4). BRTO has been mostly employed as a primary prophylaxis method; however, in one single study, BRTO was shown to achieve a high haemostatic rate after controlling the initial bleeding episode with a balloon tamponade (33).

In summary, it does appear that the best therapeutic options for actively bleeding gastric fundic varices are



ICV: Inferior cava vein. PV: Portal vein. LRV: Left renal vein. SV: Splenic vein. SMV: Superior mesenteric vein. LGV: Left gastric vein. IGV1: Type 1 isolated gastric varices. GRS: gastro-renal shunt.
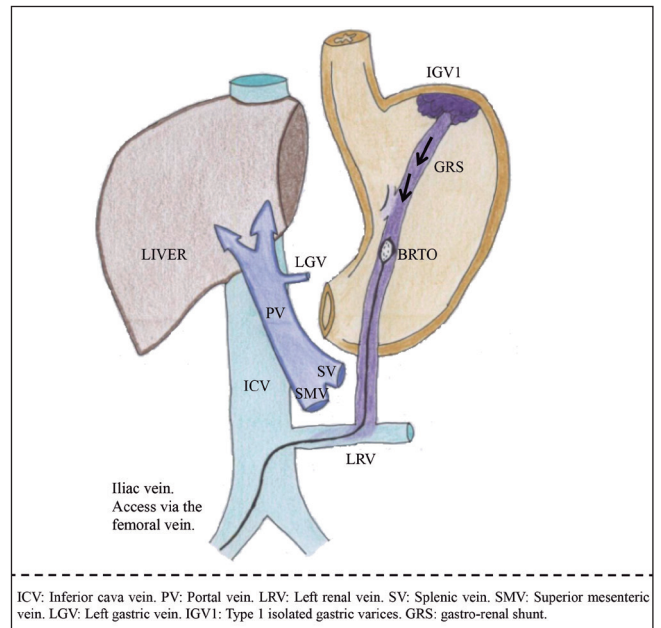
Fig. 4. BRTO (balloon-occluded retrograde transvenous obliteration). Access and technique.

CA injection and TIPS (9,31,32). The international consensus on portal hypertension held in 2015 (Baveno VI) recommended CA injection as the first therapeutic option (1;A) (10), while TIPS should be considered as the second option, and indicate it only when CA injection fails or after balloon deflation (2;B) (30,31).

**Secondary prophylaxis**

It has been estimated that the rebleeding rate of fundic varices is close to 15% (1-3). Some studies have demonstrated that CA injection is the most effective endoscopic technique for secondary prophylaxis, superior to endoscopic band ligation and/or ethanol injection (3,6). The usefulness of non-selective beta blockers in this setting remains controversial. In a clinical trial comparing CA injection and non-selective beta blockers for secondary prophylaxis of fundic varices, CA injection proved to be

**Table II. Efficacy of urgent TIPS in acute bleeding of fundic varices**

| Author, year (ref.) | n | Type of varix | Urgent (%) | Hemostasis (%) | Rebleeding (%) | Mortality (%) |
|---|---|---|---|---|---|---|
| Stanley, 97^ (26) | 106 | Fundic* (66%) | 34 | 96 | 16 | 40 |
| Chau, 98^ (27) | 112 | Fundic* (26%) | 100 | 96 | 24 | 43 |
| Barange, 99^ (28) | 32 | GOV1 (69%) GOV2 (31%) | 63 | 90 | 28 | 60 |
| Tripathy, 02^ (29) | 40 | Fundic* (40%) | 58 | 100 | 41 | 21 |

Ref: Reference; n: Number of patients. *These studies do not explain the type of fundic varix (IGV1 or GOV2). ^All studies used bare TIPS.

more effective in terms of rebleeding and overall survival (34). In another study, authors demonstrated that the addition of non-selective beta blockers to CA injection for secondary prophylaxis does not appear to reduce rebleeding rate or improve survival (35). However, other reports have shown a better survival in those patients treated with the combination of CA injection and a non-selective beta blocker (36).

On the other hand, there is strong evidence supporting the use of TIPS for secondary prophylaxis (as well as CA injection) (1,6). However, studies evaluating the efficacy of TIPS for this indication did not include patients with fundic varices. The TIPS has shown a high efficacy and a similar rebleeding rate than CA injection, with no significant differences in terms of survival (37,38). As TIPS may associate a greater morbidity than CA injection (37), and as shown in one study CA injection is probably more cost-effective (38), there is an important question that remains unanswered: Should we indicate a TIPS to all patients that have a history of bleeding from fundic varices, or on contrary we should only offer this alternative to those patients in whom CA injection has already failed (3).

The international consensus on portal hypertension of the year 2015 (Baveno VI) (13) recommends that to prevent rebleeding from gastric varices, consideration should be given to additional glue injection (after 2 to 4 weeks), beta-blocker therapy or both combined, or TIPS. Other options of therapy may include BRTO (in case of TIPS contraindication or technical difficulties) (40,41), or derivative surgery, but these therapeutic alternatives should be carefully considered in a case by case approach, depending on patient characteristics (degree of liver dysfunction) and surgeon skills (1,3).

## TECHNICAL ASPECTS OF CYANOACRYLATE INJECTION

Among other potential indications for glue injection in the field of Gastroenterology, the most useful application of this type of therapy is the treatment of fundic gastric varices (42). There are different types of glues (Table III), but all of them have in common that CA is part of their chemical composition. CA posses the characteristic of becoming solid very quick when it gets in contact with a weak base substance, like water or blood. Different trademarks of CA are manufactured by different companies. The differences among them are mainly based on chemical variations in the length of alkyl group, which may alter the physicochemical properties of the agent. For this reason, some of these glues (Indermil® and Histoacryl®) have to be diluted with lipiodol in a ratio of 1:1 or 1:1.6, to reduce the polymerization speed. However other types of CA (Dermabon® and Glubran 2®) have longer polymerization times and therefore will not require dilution with lipiodol, being in our opinion easier to use (42,43). In cases in which CA is diluted with lipiodol, it should be recommended to monitor the injection by radiologic control.

The reported rate of obliteration of fundic varices after CA injection is high (90%), and the rebleeding rate oscillates between 0-15% (15,16). CA injection is a relatively safe technique; however, some reports have described a mortality of 0.5% (44). Additionally, it should be mentioned that a number of adverse effects have been described with CA injection: Chest pain, fever, rebleeding due to CA extrusion (Fig. 5), splenic infarction, portal and
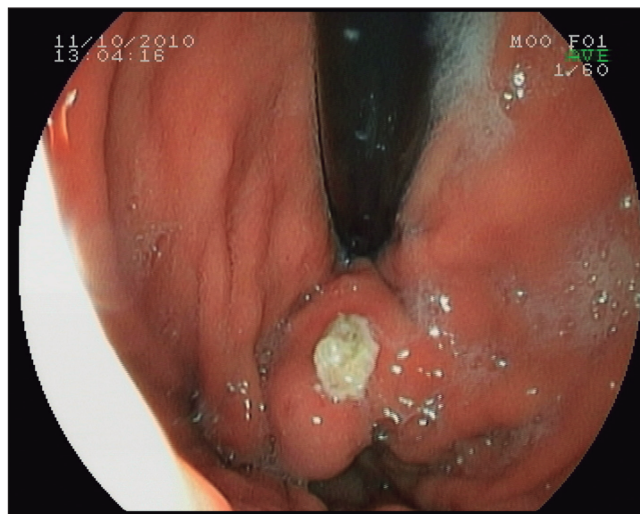


Fig. 5. Glue extrusion from a fundic varix.

Table III. Characteristics of different types of cyanoacrylate available in the management of fundic varices

| Trade name | Manufacturer | Active component | Dosage | Lipidol dilution need | Polymerization |
|---|---|---|---|---|---|
| Indermil® | Covidien | N-butyl-2-cyanoacrylate | 0.5 cc | Yes | Fast |
| Histoacryl® | TissueSeal | N-butyl-2-cyanoacrylate | 0.5 cc | Yes | Fast |
| Dermabond® | Ethicon | 2-octyl-cyanoacrylate | 0.5 cc | No | Slow |
| Glubran2® | GEM, Italia | N-butyl-2-cyanoacrylate | 0.25 cc; 0.5 cc; 1 cc | No | Slow |

splenic veins thrombosis, sepsis, fistulae, etc. One of the most feared adverse effects associated with this type of treatment is the embolization of the CA injected. In a study in which a CT-scan was systematically performed after CA injection, results disclosed that 47% of patients had pulmonary embolisms of CA, but only 1% was symptomatic. If the patient has arteriovenous pulmonary shunts or a patent foramen oval, systemic embolization to other distant regions may occur (42-46). A number of factors have been associated with an increased risk of embolization: a) Injection in IGV1; b) rapid injection; and c) overdilution with lipiodol (43).

We believe that to do the best work at CA injection, one should have an adequate understanding of the indications, be familiar with the technique and with the type of CA used, and have a good coordination with the auxiliary personnel. On table IV, a detailed description of every step required for CA injection is shown. As we do in our general practice, we recommend the use of a CA type that does not require dilution with lipiodol.

After retrieval of the needle from the varix, a back-bleeding may be observed. Before doing another injection to achieve hemostasia, we recommend to wait and observe for a while, as CA haemostatic effect is not instantaneous. The majority of studies published in the literature have employed dosages of 0.5-1 ml of CA, without observing clinical differences between dosages. Although there is no supporting evidence for such a practice, most authors

### Table IV. Endoscopic technique of cyanoacrylate injection

*Material required: (It should be prepared and checked before the injection)*

1. Needle catheter  (2 or 3)
2. Key of 3 connections
3. Syringe of 10 ml completely filled with distilled water (2-3 syringes)
4. Syringe of 2 ml filled with 0.5-1 ml of CA (as many syringes as CA phials will be injected)
5. Conventional scissors
6. Acetone
7. Protective glasses for all staff

*Steps for a high quality CA injection: (Endoscopist functions in cursive. Auxiliary staff functions underlined)*

1. *Characterize with the endoscope the varix or varices to be treated (usually from the stomach and in retroversion view)*
2. *Define the ideal injection point trying different movements with the endoscope and the needle catheter*
3. *Place the key of 3 connections in the proximal end of the needle catheter*
4. *Place simultaneously in the other 2 connections of the key, the syringe with 5-10 ml of distilled water and the syringe with 2 ml of CA*
5. *Enter the needle catheter, purged with distilled water, through the biopsy channel of the endoscope*
6. *Puncture the varix carefully and softly in the desirable site and inject 2-3 ml of distilled water* in order to check that the needle is inside the varix (a slight elevation of the varix could be seen when destilled water is injected)
7. When a good position of the needle has been checked, *the key should be moved to the CA syringe and 0.5-1 ml of CA should be injected.* That CA will be temporally inside the catheter
8. *Immediately, the key should be moved to the connection where destilled water syringes are placed, and 3-4 ml should be injected* to push cyanoacrylate form the interior of the catheter to the interior of the varix
9. Once 3-4 ml of destilled water has been injected, *the endoscopist should advance the endoscope maintaining the retroversion view, in order to move away the varix and removing the needle from it.* It is very important *not to hide the needle inside the plastic catheter neither hide the catheter inside the endoscope´s work channel*
10. *Simultaneously* as described in *point 9,* auxiliary staff should *inject continuously destilled water through the needle to prevent its tamponade* (just in case another injection would be necessary)
11. Retroversion is subsequently undone, without removing the catheter *(which will protrude 4 cm through the distal end of the endoscope´s work channel).* The endoscope is removed from the patient
12. *Once removed (the needle is advanced and cut leaving a security margin at the distal end of the endoscope of 3 cm)* and only in that moment the catheter can be safely removed from the endoscope´s work channel
13. Finally, *the endoscope´s work channel is washed with water and the endoscope´s lens is cleaned with a piece of cotton impregnated with acetone*

will recommend, for safety reasons (systemic embolization risk), not to use more than 1-2 ml of CA per session (47,48). There are still some questions that need to be answered, and hopefully we will have definitive answers for them in coming years: a) Which type of CA is the most effective?; b) what should be the ideal amount/volume of CA that should be injected per varix and session?; c) in case of using a type of CA with fast polymerization, which dilution rate would be the best one?; d) should intravascular injection of CA be checked by radioscopy or with an echoendoscope?; and e) what is the best way to confirm that the varix has been obliterated (gentle pressure with a plastic catheter *vs.* endoscopy-ultrasound with Doppler), and how much time should we wait before doing it?

Finally, it should be mentioned that there are other sclerosing agents, like thrombin or fibrinogen that may potentially be as efficacious as CA. Unfortunately, little information is available in the literature, preventing from widespread use of them in clinical practice.

## ENDOSCOPIC ULTRASOUND (EUS) IN FUNDIC VARICES

The diagnosis of gastric fundic varices by means of standard upper gastrointestinal endoscopes may be sometimes really difficult, mainly in those cases of small size or by misdiagnosing them as thickened gastric folds. In those uncertain cases, EUS with the help of the Doppler function might be helpful to further clarify the diagnosis, proving a definitive diagnosis if intravariceal flow or venous flow is demonstrated (43).

EUS has been proposed as having some theoretical advantages for CA injection. EUS allows one for real-time confirmation of appropriate delivery of CA into the varix lumen, permits to monitor the entrance of the CA in the varix, and it may be performed even in those cases in which there is no option to obtain a direct endoscopic visualization of the varix for injection. Moreover, it has been postulated that the identification and selective injection of CA in the main perforator feeding vein may reduce the amount of glue needed to achieve varix obliteration, reducing the potential risk of embolization. However, this theoretical advantage has not been adequately demonstrated and, from a practical point of view, it may be technically challenging (44,49).

Other authors have proposed that EUS may also allow one to inject CA in fundic varices through a transesophageal approach (in those cases with no esophageal varices). This may avoid retroflex therapy of fundic varices that in certain cases may be difficult or not technically possible. This technique would also avoid back-bleeding when removing the needle from the varix as it has been postulated that the diaphragm and the esophagus wall would act as a compressive barrier for the varix (50). However, this theoretical advantage of EUS is yet to be demonstrated.

Recent publications have shown that the combination of EUS-guided CA injection in conjunction with intravarix coil deployment may be technically feasible. Initial coil placement may theoretically produce a partial thrombosis of the varix, with the intention of requiring a smaller amount of CA to achieve a complete obliteration of the gastric varix afterwards. This novel combined approach has been shown, in preliminary reports, to have a good efficacy and a reasonable complication rate (48-50). However, more scientific evidence is still required before one may confidently recommend its use in clinical practice.

Despite the aforementioned theoretical advantages of EUS guided treatment of gastric varices (injection of CA in the perforator feeding veins, use of coils combined with CA, possibility of using a transesophageal approach for CA injection), and based on our clinical experience and existing evidence, we believe that the only demonstrated utility of EUS in the treatment of fundic varices is to confirm its diagnosis in uncertain cases after endoscopy, and to monitor (with the Doppler) if the varix has been obliterated after CA injection or a second session is required. It is our believe that other indications proposed for EUS in this setting should be considered investigational at present time.

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