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EUS–guided Cyanoacrylate injection versus standard endoscopic technique in the obturation of high risk gastric varices

Thesis

Submitted for partial fulfillment of MD Degree in Hepatology and Gastroenterology

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Introduction

Gastric varices occur in around 20% of patients with portal hypertension, mostly secondary to liver cirrhosis. Although they bleed less frequently than oesophageal varices, gastric variceal bleeding tends to be more severe with reported higher mortality of approximately 45% (**Wani et al**., **2015**). High risk gastric varices include presence of any of the following risk factors (**Triantafyllou and Stanley**, **2014**):

- Location of gastric varices (IGV1>GOV2>GOV1).
- Size of fundal varices >10 mm.
- Severity of liver failure (Child class C>B>A).
- Endoscopic presence of variceal red spots.

Standard endoscopic management of gastric varices is endoscopic intravariceal cyanoacrylate (CYA) injection for treatment of acute bleeding, as well as for secondary prophylaxis (**Al–Hillawi et al**., **2016**).

Endoscopic variceal obliteration (EVO) by direct endoscopic injection (DEI) using tissue adhesives like glue, CYA or histoacryl has provided a positive direction to management of GVs. CYA is a polymer which upon coming in contact with blood polymerizes instantly leading to obliteration of varices. It is called "obliteration" and not "eradication" since the varices may be still visible post treatment. EVO with N-butyl-2-cyanoacrylate has been the advocated first-line method in managing the gastric varices especially fundic varices (**Girotra**, **2014**).

EVO by DEI using CYA demonstrated higher hemostasis and lower bleeding rates compared to band ligation or sclerotherapy. Nevertheless, CYA treatment is known to be associated with significant adverse events like para-variceal injection, hemorrhage from post injection ulcer, needle sticking in the varix, intra-peritoneal injection leading to peritonitis and adherence of the glue to the endoscope, fever, embolization into the renal vein, IVC, pulmonary or systemic vessels. (**Belletrutti et al**., **2008**).

Pulmonary embolism due to CYA therapy is a serious complication and sometimes fatal. Pulmonary embolism appears to be more common in patients receiving a higher volume of cyanoacrylate during the injection procedure (**Hwang et al**., **2001**).

In recent years, the role of endoscopic ultrasound (EUS) has expanded rapidly into the therapeutic arena. EUS offers unique access to abdominal arterial and venous vasculature that until now has only been accessible to surgeons and/or interventional radiologists. This has had the most clinical impact on the treatment of gastroesophageal varices, where EUS may play a role both in the acute and elective management and can deliver therapy in the form of glue injection, endovascular coil placement or a combination of the two (**Hall et al**., **2017**).

EUS enables an assessment using Doppler to confirm vessel obliteration after treatment. However, targeting the perforating feeder vessel rather than the varix lumen itself may theoretically minimize the amount of CYA needed to achieve obliteration of GVs and thereby reduce the risk of embolization (**Wang et al**., **2016**).

Romero-Castro et al. assessed the efficacy of EUS-guided CYA injection at the entrance of the perforating veins to obtain variceal obliteration in five consecutive GV patients. They thought that EUS-guided CYA injection at the perforating veins of GV would be the optimal place to do so. This produces the maximal blood flow blockage of the inflow vein with lower amounts of CYA used and avoid either more punctures or more amounts of CYA necessary to fill the varix from the inflow to the outflow veins (**Romero-Castro et al**., **2007**).

To the best of our knowledge, no studies in the literature compared standard DEI to EUS guided CYA injection into perforating veins in high risk gastric varices which represents a significant clinical challenge as it requires injection of large amount of CYA & multiple sessions which is associated with high incidence of complications.

Aim of work

The aim of present study is to compare the efficacy & safety of EUS-guided CYA injection at the entrance of the varix or the perforating veins versus DEI of CYA in treatment of high risk gastric varices.

Patients & Methods

1. Study design & Characteristics:

A single-centre, pilot randomized trial study with two arms; will be carried on patients over 1 year study period starting from June 2019 to June 2020 at the EUS Unit of the Department of Gastroenterology at Mansoura Specialized Medical Hospital, Mansoura University (Egypt).

2. Patients:

A total of 42 patients will be included, GVs will be classified according to the Sarin and Kumar classification (**Sarin and Kumar**, **1989**) into GOV II or IGV I with recently bleeding GV & high-risk GV (defined by Baveno VI consensus for primary prophylaxis). After obtaining consent, eligible patients will be randomized in 2 groups using computer-generated random number sequences using excel software in concealed envelopes with block randomization design. Group I will undergo EUS-guided CYA injection at entrance of perforator veins. Group II will undergo DEI of CYA.

i. Inclusion criteria:

- Above 18 years old patients
- High risk GOV II and IGV I varices (>10 mm) on initial standard diagnostic upper endoscopy
- Recent bleeding and primary prophylaxis
- Patients who are unable or unwilling to undergo alternative therapies for GV [such as transjugular intrahepatic portosystemic shunts (TIPS) or surgery], or prior TIPS had failed.

ii. Exclusion criteria :

- Inability to give informed consent for the procedure.
- Concurrent hepatorenal syndrome and/or multiorgan failure.
- Presence of HCC &/or portal vein thrombosis.
- Previous endoscopic treatment for GVs.

- Platelet count less than 50,000/ml or International Normalized Rate (INR) >2
- Esophageal stricture
- Previous esophageal or gastric surgery.
- Pregnancy.

iii. Sample size

Sample size was calculated by PASS software for Windows (version 11.0.8).

The reported rate of obliteration of fundic varices after CA injection is high (90%) in control group (**Martínez-González et al**., **2015**), and we hypothesized this rate to be 99% in EUS group.

Group sample sizes of 201 in group one (EUS group) and 201 in group two (control group) achieve 99% power to detect a difference between the group proportions of 0.1000. The proportion in group one (the treatment group) is assumed to be 0.9000 under the null hypothesis and 1.0000 under the alternative hypothesis. The proportion in group two (the control group) is 0.9000. The test statistic used is the one-sided Z test with pooled variance. The significance level of the test was targeted at 0.0100 .

According to **Connelly** (**2008**), a pilot study sample should be 10% of the sample projected for the larger parent study.

For this current pilot study, it will be conducted on 10% of these admissions, so we need 21 cases for this pilot study in each arm (case and control groups).

3. Outcomes:

The primary outcome of the study will be to compare the technical success defined as complete variceal obliteration and complications rate including bleeding, pulmonary embolism (PE), ulcers, fever, paravariceal

injection & rebleeding. Secondary endpoints will be amount of cyanoacrylate used & number of sessions.

4. Methods:

Each patient will be subjected to :

- Written informed consent will be obtained from each patient, including a discussion on the procedure.
- Clinical assessment including history taking and physical examination
- Routine laboratory investigations including complete blood picture and serum creatinine.
- Liver function profile (serum bilirubin, AST, ALT , albumin and prothrombin time).
- The severity of underlying disease will be assessed by the Child-Turcotte-Pugh score (CTP) based on serum albumin, bilirubin, prothrombin time, the presence of ascites and encephalopathy.
- All procedures will be performed under deep sedation or general anesthesia in the left lateral position.
- Intravenous antibiotics will be administered to all patients prior to the endoscopic procedure to minimize the risk of secondary bacterial infection. Oral or intravenous antibiotics will be continued for at least 3 days following variceal injection.

✓ **Endoscopic procedure and technique**:

- Standard diagnostic upper endoscopy will be performed in order to classify the varices according to the classification of Sarin and Kumar. Only high risk GOV II and IGV I varices (>10 mm) will be included.
- EUS examination will be done in all patients with a Pentax linear Echoendoscope EG3870UTK (PENTAX medical, Tokyo, Japan) attached to a Hitachi Avius ultrasound system (Hitachi Medical Systems, Tokyo, Japan). All EUS examinations will be done by two endosonographers. The echoendoscope will be positioned in the

distal esophagus at the level of the cardia to visualize the gastric fundus and intramural varices.

- EUS will be used to display the vascular anatomy, in particular the feeding vein. GVs will be classified endosonographically according to Boustière et al which considered size of GVs and gastric wall abnormalities (**Boustière et al**., **1993**):

  1: Size of GVs:

  - Grade 0 (none)
  - Grade 1 (small or non-confluent varies < 5 mm)
  - Grade 2 (large or confluent varices ≥ 5 mm)

  2: Abnormalities of gastric wall:

  1. Grade 0 (none)
  2. Grade 1 (thickening and brilliance of the third hyperechogenic layer with or without fine internal anechogenic structures).
  3. Grade 2 (visible vessels in the third layer which deform the entire wall, with penetrating varices).

- EUS-guided injection of CYA will be done at entrance of of the varix or the perforator veins when identifiable using a mixture (1:1) of 2-octyl-cyanoacrylate & lipidol using 19G EUS-FNA needle in Group I, or DEI of CYA in Group II.

✓ **Follow-up after endoscopy**:

After the procedure, patients will be observed for 2 hours in the recovery room before being discharged. Endoscopic examination and Doppler EUS will be repeated in all patients at 3, and 6 months post-procedure (or sooner with recurrent bleeding) to confirm eradication. Hemostasis, early post treatment bleeding and late post treatment bleeding will be recorded according to Baveno VI concensus.

GVs will be considered obliterated by direct endoscopy when not visible and/or hardened to catheter palpation. Obliteration by Doppler EUS will be considered by visualization of clot and absence of Doppler

flow within the gastric wall. Repeat injection will be performed in the absence of obliteration. Direct endoscopic and Doppler EUS examinations will be repeated again at 3, and 6 months after each injection.

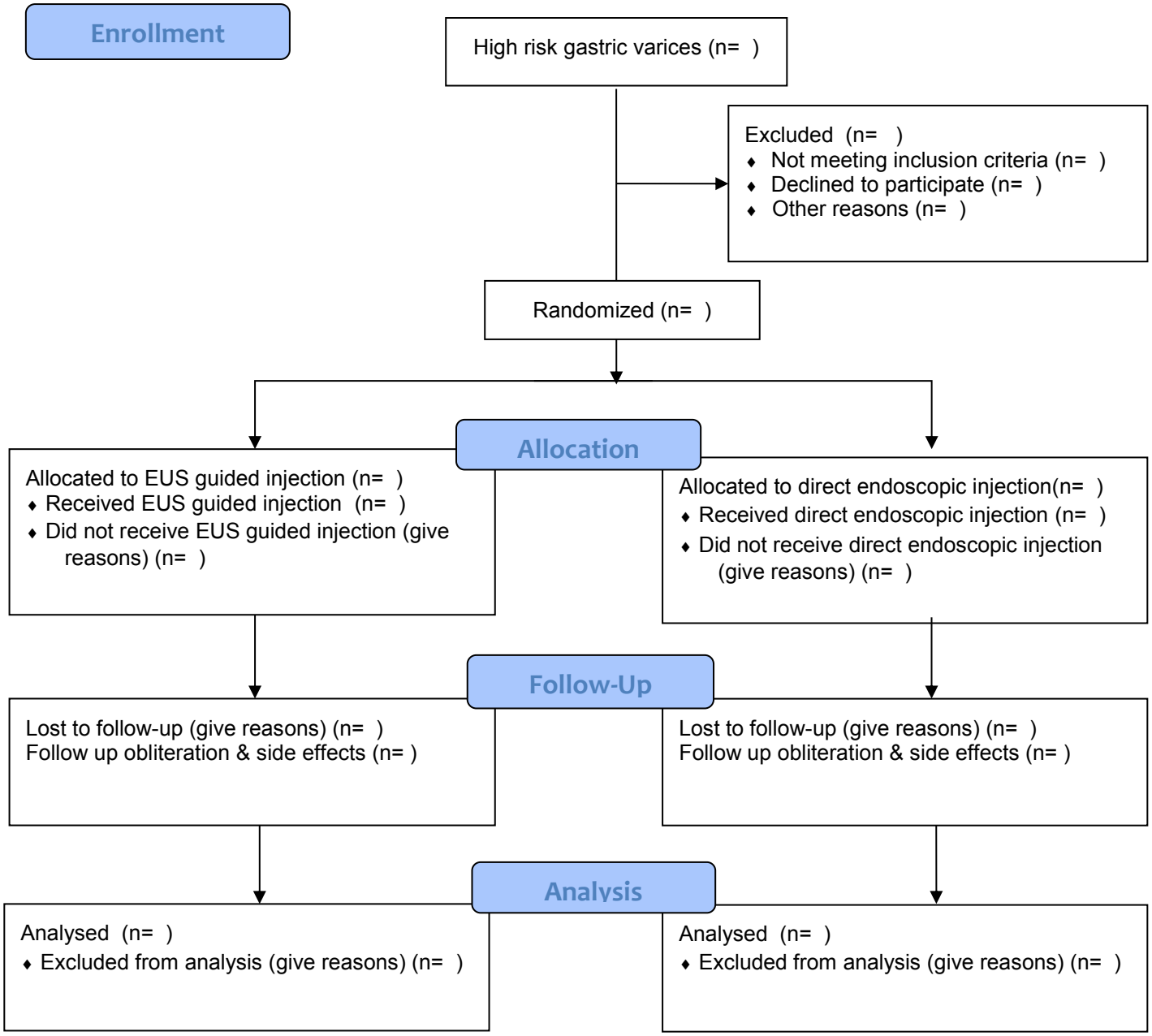
Ethical considerations:

Study protocol will be submitted for approval by the medical ethics research committee, faculty of medicine, Mansoura University.

Informed written consent will be obtained from each participant in the study after assuring confidentiality.

Statistical analysis:

The collected data will be coded, processed & analyzed using SPSS program for windows. The appropriate statistical tests will be used when needed. The level of significance will be considered at 5% ($P \leq 0.05$).


Enrollment
High risk gastric varices (n=)
Excluded (n=)
♦ Not meeting inclusion criteria (n=)
♦ Declined to participate (n=)
♦ Other reasons (n=)
Randomized (n=)
Allocation
Allocated to EUS guided injection (n=)
♦ Received EUS guided injection (n=)
♦ Did not receive EUS guided injection (give reasons) (n=)
Allocated to direct endoscopic injection(n=)
♦ Received direct endoscopic injection (n=)
♦ Did not receive direct endoscopic injection (give reasons) (n=)
Follow-Up
Lost to follow-up (give reasons) (n=)
Follow up obliteration & side effects (n=)
Lost to follow-up (give reasons) (n=)
Follow up obliteration & side effects (n=)
Analysis
Analysed (n=)
♦ Excluded from analysis (give reasons) (n=)
Analysed (n=)
♦ Excluded from analysis (give reasons) (n=)

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