

## Comparative study of tissue adhesive therapy versus band ligation in control of actively bleeding esophageal varices

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### Abstract

**Background and study aims :** Bleeding esophageal varices is a common life-threatening emergency that carries a significant morbidity and mortality. Acute variceal bleeding is considered active when spurting and/or oozing varix is seen at the time of endoscopy, or inactive in the presence of large esophageal varices with blood in the stomach with no other bleeding source at the time of endoscopy. Aim: comparing endoscopic variceal ligation (EVL) versus cyanoacrylate injection (CI) in active esophageal variceal bleeding control.

**Patients and methods :** a retrospective single tertiary center study from April 2014 to February 2018, including 401 patients with active esophageal variceal bleeding.

**Results :** Endoscopic hemostasis was achieved by both endoscopic variceal ligation in 182 patients (91.9%) and cyanoacrylate injection in 197 patients (97.05%) without significant difference (P value 0.15). Re-bleeding occurred more frequently in EVL group 20 patients (10.1%) compared to 14 patients (6.9%) in CI (P value 0.01). Early six-week Mortality was higher among EVL group (20.7%) compared to CI (17.2%) without statistical significance (P value 0.3).

**Conclusion :** Both EVL and CI are almost as effective in achieving endoscopic hemostasis. CI is more effective, feasible, and could be used as a salvage therapy and/or spared for risky active bleeding esophageal varices. (*Acta gastroenterol. belg.*, 2020, 83, 5-10).

**Key words :** bleeding esophageal varices, endoscopic hemostasis, variceal ligation, and cyanoacrylate.

### Introduction

Active esophageal variceal bleeding represents a medical challenge, that Carries a significant morbidity and mortality (1,2). Acute variceal bleeding is defined as bleeding from an esophageal varix, or the presence of large esophageal varices with blood in the stomach and no other source of bleeding at the time of endoscopy (3). Its difficulty is mainly due to the critical condition of the patient which necessitates immediate intervention and also the bloody endoscopic view field in the presence of spurting or oozing varices (as shown in Fig. 1).

Incidence of six-week mortality is approximately 15-20% with each attack of variceal bleeding. The more severe the liver disease the higher the mortality, ranging from 0% in patients with Child-Pugh class A disease to 40% in patients with Child-Pugh class C (4), Mortality has decreased steadily since the 1980s, from 40% to be about 10-20% (5). This is mainly due to proper resuscitation, increasing use of vasoactive drugs, therapeutic endoscopy, and antibiotic prophylaxis

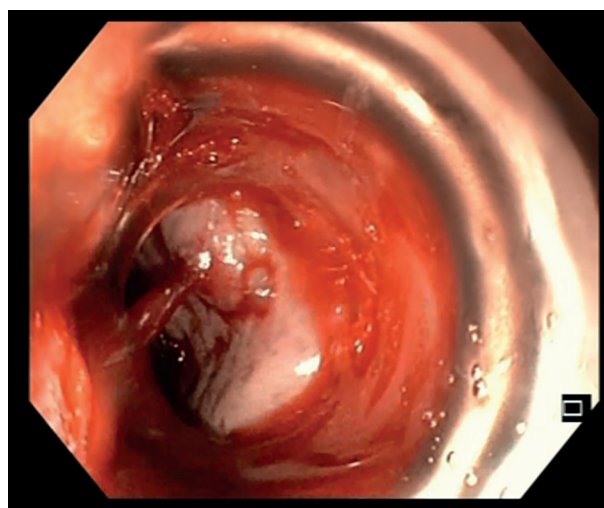


Fig. 1. — Active bleeding esophageal varix : spurter.

(5). However, early six-week mortality is still the same in Child–Pugh C patients. Early mortality within six-week is related to severity of liver disease, portal vein thrombosis (6), active bleeding on admission (7), and presence of infection (8).

Most of the Guidelines, such as ASGE, recommend endoscopic variceal ligation (EVL) as the preferred endoscopic method for acute variceal bleeding and sclerotherapy (SCL) is used for cases where band ligation is difficult or unavailable, as most of the previous studies include patients with both active and inactive variceal bleeding, without specifying which method is better for endoscopic hemostasis in cases of active bleeding (3, 9).

Band ligation may not be always feasible in active variceal bleeding as blood may obscure the endoscopic view field in the presence of band set (see fig. 2), but once applied properly it achieves good endoscopic hemostasis with few adverse events. Cyanoacrylate injection (CI) targeting the bleeding varix with the injector needle may be an easy and preferable method for control of active bleeding varix but multiple injections may be needed. We

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Submission date : 14/02/2019  
Acceptance date : 20/04/2019

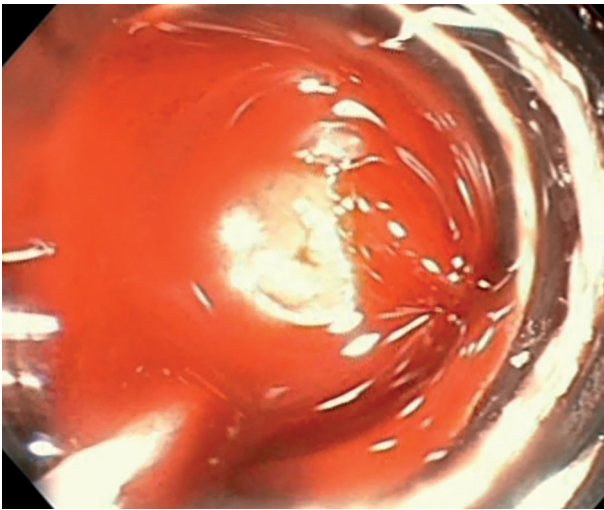


Fig. 2. — Active bleeding varix within the Banding cap. Difficult bloody endoscopic field of view within banding cap may hinder the proper capture of the bleeding point.

conducted this study to compare between both techniques in control of active esophageal variceal bleeding.

## Materials and methods

### Primary outcome

This study aims to compare between EVL and CI in management of active esophageal variceal bleeding regarding achieving endoscopic hemostasis, incidence of re-bleeding after initial hemostasis and early mortality within six weeks of the initial episode of bleeding.

### Patient and methods

This is a retrospective single tertiary center study, from April 2014 to February 2018, the study was approved by the local ethical committee of Kasr Alainy School of medicine on 10 April 2018, and written informed consent was obtained from all patients. The study protocol conforms to the ethical guideline of 1975 Declaration of Helsinki.

7560 patients were admitted to internal medicine department, Cairo university hospitals, with acute upper gastrointestinal bleeding. 543 patients of them presented with active esophageal variceal bleeding. In 223 of them band ligation was done and tissue adhesive therapy was performed for 320 patients. 142 patients were excluded as they had incomplete data. (See patients' distribution in fig. 3)

The remaining 401 one patients with complete data were included in our study, Band ligation was done for 198 patients, while cyanoacrylate injection was done for 203 patients.

All patients were admitted to hospital, received IV PPI, octreotide, proper fluid resuscitation and packed RBCs targeting hemoglobin level 7g/dl and 10g /dl for patient

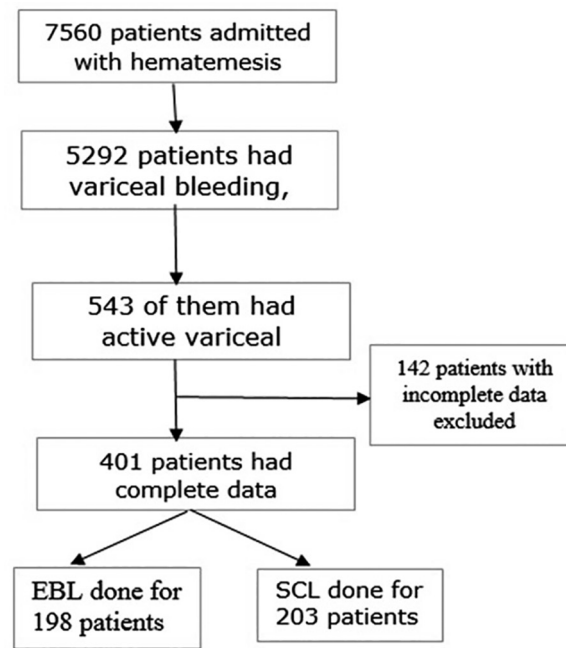


Fig. 3. — Flow chart of patients' distribution.

with Ischemic heart disease. Informed consent have been signed by all patients, endoscopy was performed after stabilization of the hemodynamic status mostly within 24 hours of admission (10-12).

### Esophageal variceal ligation EVL

Band ligation procedure was performed according to the technique protocol prescribed in EL-Ibrashi Endoscopy unit using an Olympus GIF140, 160, GIF-H170, 180 endoscope (Olympus Optical Co. Ltd, Tokyo, Japan). After the diagnostic endoscopy is performed and the culprit varix is identified and its distance from incisors is measured, the endoscope is withdrawn from the patient for assembly of the six-shooter multi-band kit (MBL-6, Cook Inc., Winston-Salem, USA). Attempts were made to ligate the active bleeding varix on the rupture point. The first step is getting clear endoscopic field by proper patient positioning, adequate washing and suction then getting proper position by opposing the bleeding point, suction and make sure of capturing the culprit varix within the banding cap, lastly applying the band. Adequate endoscopic hemostasis is ensured by a clear field view after capturing the bleeding point (13). Then the other varices were lighted at the same session.

### Cyanoacrylate injection CI

Cyanoacrylate injection was performed by introduction of the injection needle through the working channel of the gastroscope then getting a proper position by adjusting the scope till the bleeding point is in alignment with 7 O'clock, then tissue adhesive solution N-butyl-2-cyanoacrylate (Histoacryl®) was injected. Each injection contained a mixture of 0.5 mL cyanoacrylate and 1 mL

Lipiodol® (Guerbet Laboratory, Aulnay-Sous-Bris, France) and the total dose of 1.5 mL cyanoacrylate was injected into the lumen of the bleeding varix, followed by flushing the injector needle by 2 ml of distilled water to push the glue into the varix then withdrawing the needle. Obliteration of the varix can be checked by probing with the injector teflon, the obliterated varix feels firm whereas normal varix is soft (14).

#### Secondary prophylaxis

After primary endoscopic hemostasis all patients scheduled for secondary prophylaxis session with band ligation starting from 3-4 weeks after initial hemostasis. All procedures were performed by well-experienced endoscopists with the same level of experience.

Data were recruited from medical records and endoscopic database; patients with incomplete data were excluded. Data were collected regarding admission data, age, sex, vital signs, hemoglobin level, blood transfusions, causes of portal hypertension, time of endoscopy (1<sup>st</sup> day or 2<sup>nd</sup> day of admission), size of the varices, Child Pugh score, hospital stay, failure to control active bleeding, incidence of re-bleeding, early mortality within six weeks of the initial episode of bleeding.

#### Statistical analysis

Descriptive statistics were done; numerical data are presented as mean (SD) and categorical data as frequency and percentages. Continuous variables were tested for normality by the Shapiro-Wilk normality test. For the comparison between the 2 groups, normally distributed data were analyzed using independent samples T-test. Data found to be non-normally distributed were analyzed using the Mann-Whitney U test. The Chi-squared test or Fischer's exact test was used to compare percentages

between different groups of patients. Univariate and multivariate logistic regression models were performed to identify independent predictors of six-week mortality. Data analysis was done using Statistics/Data Analysis (STATA) version 13.1 software.

#### Results

Four hundred and one patients with active variceal bleeding were included in this study. EBL was done for 198 patients (49.38%) and CI for 203 (50.62%), the mean age of the studied population was 55±10.03 years, male to female ratio was 5:4. The demographic and clinical characteristics of patients from both groups are presented in table 1.

The patients in the two groups were matched regarding age, gender, demographic characteristics, size of varices, etiology of portal hypertension and severity of liver disease. They were vitally stable at time of endoscopy with serum hemoglobin level  $\geq 7$  g/dl. Endoscopy was performed in the first day of admission for 371 of patients (92.52%) and 30 patients (7.48%) in the second day, delayed for proper resuscitation. Esophageal varices were classified as small, medium, or large according to Paquet's classification (15).

Endoscopic hemostasis was achieved successfully by both EVL in 182 patients (91.9%) and CI 197 patients (97.05%) without statistical difference (*P* value **0.15**). Five patients (2.46%) among CI group required a second CI session, while among the band group bleeding was not controlled in 6 patients (3.03%) and shifted to CI that successfully controlled the bleeding as shown in table 2.

Re-bleeding occurred more commonly in EVL group (20 patients, 10.18%) compared to 14 patients (6.9%) in EVL with statistical significance (*P* value **0.01**). The source of rebleeding in CI group was post-CI ulcer in 13 (6.4%) patients and rebleeding varix in one patient

Table 1. — Baseline characteristics of the study population

	Band ligation (n=198)	CI (n=203)	<i>P</i> value
Age (years) Median (IQR)	56 (49-63)	56 (49-62)	0.8
Gender Male/Female	107/91	117/86	0.5
<b>Clinical</b>			
Systolic Blood pressure	100 (90-100)	100 (90-100)	0.9
Hemoglobin level (g/dL)	7.95 (7-9.2)	7.5 (6.9-8.9)	0.1
<b>Time of endoscopy</b> 1 <sup>st</sup> day/2 <sup>nd</sup> day	183/15	188/15	0.9
<b>Size of varices</b>			0.3
Small	37	42	
Moderate	97	110	
Large	64	51	
<b>Cause of portal hypertension</b> HCV /Bilharzial/PVT/others	128/24/13/33	150/18/9/26	0.353
<b>Child Pugh class</b> A/B/C	52/86/60	35/102/66	0.09

Numerical data presented as median (IQR)

Table 2. — Endoscopic hemostasis and early mortality

	Band ligation (n=198)	CI (n=203)	P value
Endoscopic Hemostasis Yes/ No	182/16 (91.9%/8.1%)	197/6 (97.05%/2.95%)	0.15
Re-bleeding	20 (10.1%)	14 (6.9%)	<b>0.01</b>
Six-week mortality	39(20.7%)	35 (17.2%)	0.3
Hospital stay(days)	5 (4-6)	5 (5-6)	<b>0.13</b>

Table 3. — Predictors of 6-week mortality (Univariate and Multivariate logistic regression)

	Univariate regression		Multivariate regression	
	Odds Ratio (95% Conf. Interval)	P value	Odds Ratio (95% Conf. Interval)	P value
Age	1.15 (1.10-1.19)	<0.0001	1.09 (1.04-1.13)	<0.0001
Gender Female	0.64 (0.37-1.08)	0.09		
Systolic BP	0.96 (0.93-0.99)	<b>0.04</b>	0.98 (0.94-1.03)	0.45
Hemoglobin level	0.69 (0.56-0.84)	<0.0001	0.89 (0.69-1.14)	0.37
Larger varices	2.03 (1.36-3.03)	<b>0.001</b>	1.9 (1.18-3.09)	<b>0.008</b>
Time of endoscopy 2 <sup>nd</sup> Day	2.54 (1.13-5.69)	<b>0.02</b>	1.01 (0.35-2.9)	0.98
1 <sup>st</sup> Day	1		1	
Endoscopic hemostasis	1.41 (0.31-6.41)	0.6		
Duration of hospital stay	2.89 (2.18-3.83)	<0.0001		
Higher Child Pugh class	8.73 (4.97-15.35)	<0.0001	5.71 (3.09-10.52)	<0.0001
Rebleeding	2.15 (1.16-3.99)	<b>0.02</b>		
Endoscopic technique				
Band ligation	0.76 (0.45-1.27)	0.3		
Cyanoacrylate injection	1			

(0.5%), while in EVL group post-EVL ulcer occurred in 18 (9.1%) patients and in 2 patients (1%) rebleeding from the varices was found. Re-bleeding mostly occurred 4-10 days after the first session of intervention either using EVL or CI.

The incidence of local complications such as intervention-induced ulcers was more frequent in EVL group (18 patients had post EVL ulcer), but only 13 patients had post-CI ulcer representing 9.1% of patients in CI group (*P* value 0.08).

Secondary prophylaxis sessions with band ligation started 3 weeks after initial hemostasis. Complete eradication of the varices was achieved in 62.3 % of patients after 4 sessions and 14.9% of patients required 5 sessions of EVL. Non-selective beta blocker were prescribed for all patients after stabilization of general condition aiming to decrease risk of recurrent variceal bleeding.

Early six-week mortality was lower among CI group (17.2%) compared to EVL (20.7%) without statistical significance (*P* value 0.3), there was no difference between the two groups regarding the total period of hospital stay (*P* value 0.13). patients with Child Pugh C had the greatest mortality rate (51 patients representing 71.8% of total deaths).

On univariate regression analysis, higher incidence of early six-week mortality was related to higher patient age, lower hemoglobin level, lower systolic blood pressure at presentation, higher Child Pugh score of the patient,

larger variceal size, endoscopy done on the second day and longer hospital stay. Re-bleeding was associated with almost two folds increased risk of six-week mortality (*P* value 0.02). Neither successful achievement of endoscopic hemostasis in 1<sup>st</sup> session nor the method of hemostasis, EVL or CI, affected the six-week mortality rate. (Table 3)

On multivariable regression analysis, age of the patient, size of the varices and Child Pugh score were independent predictors of six-week mortality.

## Discussion

Acute variceal bleeding may be active or inactive at the time of presentation. Active bleeding is a state which is defined endoscopically when spurting or oozing is seen from the varix (16). This discrimination between active and inactive variceal bleeding is important because the prognosis is different. The difficult bloody endoscopic view field makes many endoscopists prefer CI for rapid endoscopic hemostasis due to its excellent efficacy. CI is the optimal initial therapy for gastric variceal bleeding, however its safety and long-term results in active esophageal bleeding are still controversial (17,18).

ASGE guidelines recommend EVL as the method of choice for controlling acute variceal bleeding in general without specification whether in active or inactive variceal bleeding (19), and suggest that sclerotherapy



(SCL) is a successful method in controlling actively bleeding varices (20,21).

Significance of active bleeding has evolved from Baveno I (16), while in Baveno III (22) consensus considered it as a poor predictor for endoscopic hemostasis and high incidence of rebleeding, while its prognostic value for mortality was unclear (23).

As a tertiary referral center of endoscopy in Egypt, with high incidence HCV and subsequently Liver cirrhosis, we have many patients admitted with bleeding esophageal varices, large number of them present with active variceal bleeding, and dealing with such number of cases raised the issue to conduct this comparative study (23).

Our study showed that both techniques are almost as effective in controlling active variceal bleeding, CI was feasible in (100%) cases and rescued 6 patients when EVL failed but with more adverse events. EVL was less costly with some technical imperfections as it was not feasible in all cases; band set may limit the endoscopic vision and if the bleeding point is not perfectly captured, the bleeding may worsen and the applied band may hinder the second endoscopic interventions (24) (fig. 4). Therefore, cyanoacrylate injection will be considered a "salvage" therapy for immediate bleeding control and / or spared for high risk patients with difficult endoscopic procedure.

To the best of our knowledge there are few comparative studies directly comparing band ligation and tissue adhesive therapy in active esophageal bleeding; most of studies compare EVL versus SCL in acute variceal bleeding including both active and inactive bleeding. Ljubičić et al (25) compared EVL versus CI in management of acute variceal bleeding, 22 patients in CI group (90.9% of them with active bleeding, spurting or oozing) and 21 patients in EVL group (52.4% with active bleeding). There was no difference between the two methods in achieving endoscopic hemostasis, rebleeding, adverse events or mortality. The authors concluded that CI can be used effectively in acute variceal bleeding in whom EVL is not feasible. Duvall et al. (26) found that cyanoacrylate is as effective as band ligation in bleeding control. Sung, et al.(27) reported same success in initial hemostasis but EVL was more effective in variceal eradication.

Regarding EVL and SCL, results of 6 randomized, prospective trials reported that EVL is superior to SCL for eradicating varices more rapidly, with less recurrent bleeding and fewer adverse events (28-30). Meta-analysis comparing the use of sclerotherapy and band ligation was published in 2006 (31), involved 12 studies with a total of 1309 patients. The efficacy of endoscopic SCL for initial hemostasis was about 95%, whereas EVL efficacy was found to be 97%. No difference in mortality was found, and these authors concluded that both EVL and SCL can be used effectively for the control of acute variceal hemorrhage (31). Another meta-analysis published in

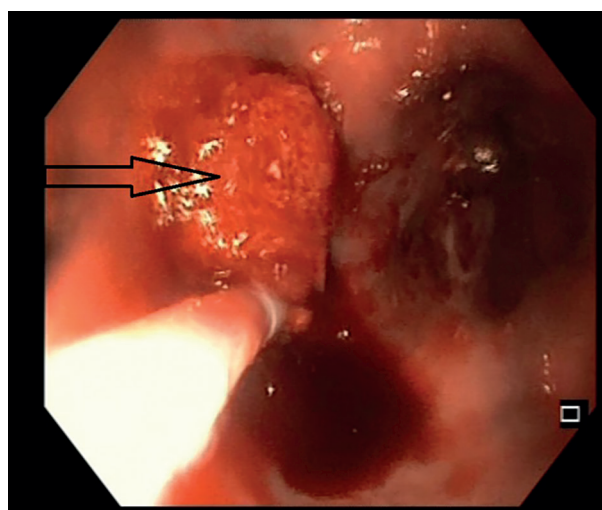


Fig. 4. — Misplaced Band ligation on active bleeding esophageal varices. Rescue tissue adhesive injection after failed band ligation (arrow).

2015 included 14 studies with 1236 patients revealed significantly lower incidence of rebleeding, adverse events and higher variceal eradication rate in EVL group than that in SCL group. But there was no significant difference in mortality between both groups (32).

In the present study the efficacy of tissue adhesive therapy (CI) in initial endoscopic hemostasis of active bleeding varix was 97.05% approaches that of EVL 92%, however technical failure rate was higher in EVL group, 6 patients (3.03%) were shifted to SCL, while in CI no one shifted to EVL.

Incidence of rebleeding was significantly lower in CI group (6.9%) than EVL group (10.1%). Most of rebleeding was due to post treatment ulcers, most of them were managed conservatively. Re-bleeding in EVL group was seemingly higher due to targeting multiple varices at the same session using 4-6 rubber bands (applied to the bleeding varix and the rest of the varices) resulting in multiple post-banding ulcers compared to post-CI ulcer which was usually a single ulcer at the site of the injection.

There was no significant difference in six-week mortality rate between the EVL group (20.7%) and CI group (17.2%). The rate of mortality in our study is less than that in literature, 22.8% in EVL (29). This may be attributed to patient population, large number of cases and higher success rate of initial hemostasis.

The incidence of local complications, included in this study treatment-induced ulcers and stricture, was less frequent in CI group (6.4% of the patients), than that in EVL group (9.1% of patients).

Mortality is increased with larger variceal size, endoscopy delayed to the second day for patient resuscitation and longer hospital stay. Rebleeding was associated with almost two folds increased risk of six-week mortality (P value 0.02). Early mortality rate was not affected by the method of hemostasis used, EVL

or CI, or by the need for second endoscopic session to achieve hemostasis.

This study was for short term results. Suggesting that: EVL is technically difficult in active bleeding, but it is feasible and efficient in non-actively bleeding varices. EVL should be used along with non-selective beta blockers for complete eradication of esophageal varices. CI might be more beneficial in the active bleeding esophageal varices and full eradication (with EVL) should be delayed.

## Conclusion

In active esophageal variceal bleeding EVL may be technically difficult, and not always feasible. While CI targeting the bleeding varix with the injector needle, few centimeters away, allow better vision and facilitates proper positioning. So CI is considered according to this study to be more effective than EVL in control active esophageal variceal bleeding with more feasibility, and could be used as a salvage therapy and/or spared for high risk cases when rapid intervention is needed.

## Conflict of interest statement

All authors have no conflict of interest and have nothing to disclose.

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