Low molecular weight heparin does not increase bleeding and mortality post-endoscopic variceal band ligation in cirrhotic patients

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Abbreviations in order of appearance

LMWH: Low Molecular Weight Heparin

EVL: Endoscopic Variceal Ligation

PVT: Portal Vein Thrombosis

EGDS: Esophagogastroduodenoscopy

TIPS: Transjugular Intrahepatic Portosystemic Shunt

HVPG: Hepatic Venous Pressure Gradient

aPTT: activated Partial Thromboplastin Time

EtOH: Ethanol

HBV: Hepatitis B virus

HCV: Hepatitis C virus

HCC: Hepatocellular Carcinoma

HE: Hepatic Encephalopathy

H-R: Heart Rate

INR: International Normalized Ratio

VKA: Vitamin K Antagonist

GOV: Gastroesophageal Varices

IGV: Isolated Gastric Varix

PHG: Portal Hypertensive Gastropathy

MELD: Model for End-Stage Liver Disease

NASH: Non Alcoholic Steato-Hepatitis

PBC: Primary Biliary Cholangitis

PLT: Platelets

RBC: Red Blood Cells

MAP: Mean Arterial Pressure

WBC: White Blood Cells

HR: Hazard Ratio

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Author Contributions

Filippo Schepis and Marcello Bianchini: study concept and design; study supervision; critical revision of the manuscript for important intellectual content.

Francesco Vizzutti: analysis and interpretation of data; drafting of the manuscript.

Giulia Cavani, Ambra Bonaccorso, Laura Turco, Alessandro Sartini, Stefano Gitto, and Alberto Merighi: acquisition of data, technical and material support.

Federico Banchelli: statistical analysis.

Erica Villa: interpretation of data; critical revision of the manuscript for important intellectual content.

ABSTRACT

Introduction. Anticoagulants are commonly indicated in cirrhotic patients due to high rate of (pro)thrombotic conditions. Low molecular weight heparin (LMWH) is safe in patients with esophageal varices. However, the safety of LMWH is unknown in patients undergoing prophylactic endoscopic variceal ligation (EVL).

Aim. To define the 4-week risk of bleeding and death after prophylactic EVL in cirrhotic patients continuously treated with LMWH.

Methods. All EVLs performed at a tertiary Italian Center from 2009 to 2016 were retrospectively reviewed. Patients treated with LMWH were classified as on-LMWH; the remaining as no-LMWH. Endoscopic characteristics at first and index EVL (that preceding an endoscopy either showing a bleeding episode or the absence of further treatable varices) and clinical events within 4 weeks from the procedures were recorded.

Results. 553 EVLs were performed in 265 patients (in 215 as a primary prophylaxis): 169 EVLs in 80 on-LMWH and 384 in 185 no-LMWH (4.9±1.1 vs. 4.8±1.0 bands/session, respectively; p=0.796). Six patients bled (2.2%) without between-groups difference (3.8% on-LMWH vs. 1.6% no-LMWH, Log-rank p=0.291). Large varices with red marks (100% vs. 51.4%, p=0.032), number of bands (5.6±0.5

vs. 4.6±1.2, p=0.004), underlying portal vein thrombosis (66.7% vs. 23.6%, p=0.033), and creatinine (2.2±2.7 vs. 1.0±0.8 mg/dl, p=0.001) at index EVL were significantly different between bleeders and non-bleeders. Six patients died within 4-week from index EVL, without between-groups difference (2.5% on-LMWH vs. 2.2% no-LMWH, Log-rank p=0.863).

Conclusions. LMWH does not increase the risk of post-procedural bleeding and does not affect survival of cirrhotic patients undergoing prophylactic EVL.

Keywords

Endoscopic Variceal Band Ligation; Low Molecular Weight Heparin; Short-term Risk of Bleeding.

Key point box

- Anticoagulants are frequently indicated in cirrhotic patients to treat portal vein thrombosis (PVT) or other (pro)thrombotic conditions.
- Low molecular weight heparin (LMWH) is often indicated as a bridge anticoagulant in patients undergoing endoscopic procedures.
- It is not known if LMWH increases the bleeding risk associated to prophylactic endoscopic variceal ligation (EVL).
- This study shows that anticoagulant treatment with LMWH does not increase the short-term risk of bleeding and death after EVL in cirrhotic patients.

INTRODUCTION

Recent data on the coagulative status of patients with liver cirrhosis show that they are prone to thrombotic [1] as well as hemorrhagic events [2,3] and that thrombotic events are more frequent in these patients than in the general population [4,5]. Compared to thrombosis in peripheral veins, portal vein thrombosis (PVT) is a complication of cirrhosis that can cause both a worsening of portal hypertension and a reduced perfusion of the liver with serious consequences in patients with esophagogastric varices at risk of bleeding and impaired liver function [4,5]. First line treatment in these cases is anticoagulation, which includes low molecular weight heparin (LMWH) [4,5]. LMWH has also been used to prevent PVT in cirrhotic patients with esophagogastric varices obtaining an unexpected favorable impact on the risk of decompensation and death [6].

It has been demonstrated that anticoagulants do not increase the risk of death associated to acute upper-gastrointestinal bleeding in patients with cirrhosis [7]. However, management of anticoagulation therapy in patients scheduled to endoscopic variceal ligation (EVL) for primary or secondary prophylaxis of variceal bleeding is still a matter of debate due to the lack of dedicated studies [4,5,8-10]. Anticoagulants are frequently stopped or the endoscopic procedure is delayed/contraindicated fearing causal hemorrhagic complications. Major concern is that anticoagulants may worsen bleeding from post-banding ulcers [11,12], which, with a risk ranging from 0.5% to 3% in primary prophylaxis [13], frequently occurs within two weeks from the procedure [14,15]. Available guidelines for upper endoscopic procedures in patients at high risk of procedure-related bleeding (which includes those undergoing EVL) recommend switching oral anticoagulants to LMWH during the peri-procedural period and restoring full anticoagulation 5 to 10 days after the

endoscopic treatment [16-20], when the risk of bleeding from post-banding ulcers is theoretically the highest. Moreover, no data are available about the safety of LMWH treatment administered continuously throughout more sessions of EVL until eradication is achieved.

Aim of this study is to verify the 4-week risk of bleeding and death after prophylactic EVL in cirrhotic patients under continuous treatment with LMWH.

PATIENTS AND METHODS

Patients

The Medical records of all patients who underwent upper endoscopy at the Endoscopy Unit of AOU Policlinico di Modena (Modena, Italy) from 1st January 2009 to 30th June 2016 were retrospectively reviewed.

Enrollment criteria were: a) histological or imaging-proven liver cirrhosis of any etiology, b) EVL as primary or secondary prophylaxis of variceal bleeding, c) EVL treatment started during the observational period. Exclusion criteria were: a) age below 18 or above 85 years, b) esophageal varices not well characterized at index endoscopy due to active bleeding causing bloody endoscopic field, c) placement of a transjugular intrahepatic portosystemic shunt (TIPS) for uncontrolled bleeding [21], as an early-TIPS [22], for intolerance/non response to NSBB [21, 23], and for concomitant difficult to treat ascites [21], d) EVLs performed in other hospitals during follow-up, e) anticoagulants started or withdrawn after first EVL.

Study design and definitions

In this retrospective cohort study, demographic, endoscopic and clinical characteristics of the eligible patients, were collected at the time of both first and index EVLs (see below for the definition) (Figure 1A). Esophageal varices were defined as F1, F2 or F3 with or without red signs (namely red whale marks, cherry red spots or haematocysts) according to JRSPH classification [24]. Gastric varices were classified according to Sarin [25]. EVLs were performed with an interval of 3-4 weeks [13, 21] until a) eradication or evidence of varices no more suitable for banding, b) death or liver transplantation, and c) late TIPS placement as secondary prophylaxis for persistent at risk varices after at least four EVL sessions [21]. Success of EVL (that is complete eradication or presence of varices no more suitable for banding) was confirmed by a control EGDS performed about 3 months after the last non-operative endoscopy (Figure 1A). Further EGDSs were performed in patients with evident or suspected upper gastrointestinal bleeding. Indeed, for the purpose of this study, within 4 weeks EVL-related bleeding was established if either actively bleeding ulcers (spurting or oozing) or fresh/digested blood without other possible causes of digestive bleeding were documented at an EGDS performed within 12 hours from the hemorrhage. Overall survival in the same time period was also calculated. Index EVL was defined as the banding session preceding a) an EGDS demonstrating a bleeding episode, b) an EGDS showing the absence of varices suitable of further ligation (applied to patients who did not bleed), and c) death, liver transplantation or late TIPS positioning (Figure 1A). Total mean number of bands was calculated as total number of used bands/total number of session/total number of patients. Patients already on LMWH at the time of the first banding session were classified as on-LMWH. Patients who had never received any anticoagulant during

the whole banding treatment were classified as no-LMWH. Anticoagulant dose at the time of EVL sessions was classified as sub coagulant (70 U/Kg subcutaneously bid) [26, 27] or anticoagulant (100 U/kg bid) [28]. In elective patients, the last dose of LMWH was administered at least 12 hours before the procedure. If the procedure was performed in the early morning, all elective patients received half daily dose of LMWH in the late afternoon, otherwise the treatment was restarted the following day [26, 27]. Patients taking a subcoagulant dose of LMWH during the peri-procedural period (i.e., from day -3 to day +1) [26, 27] received full anticoagulation (100 U/kg bid) for the underlying (pro)thrombotic condition in the time interval between EVL sessions. In non-elective patients (that is patients initially presenting with variceal bleeding while under anticoagulants), LMWH treatment was restarted after at least 24 hours of demonstrated bleeding control either at a subcoagulant or anticoagulant dose depending on the underlying prothrombotic risk.

When available, basal hepatic venous pressure gradient (HVPG) value was included if performed no more than 6 months before the first EVL session analyzed in the study.

The institutional review board (Comitato Etico Provinciale di Modena) gave approval to retrospectively collect clinical and endoscopic data and waived the acquisition of informed consent from patients who were no longer being followed at the time of data collection (Protocol ID: 411/17).

Statistical Analysis

Student's t test was applied to compare continuous variables, whereas chi-square test was performed for categorical parameters. Kaplan-Meier's analysis was used to estimate the cumulative risk of bleeding and probability of survival, while Log-rank

test was used to compare groups. Moreover, by means of Cox regression, Hazard Ratios (HR) for risk of bleeding and death were calculated comparing on-LMWH and no-LMWH patients. A propensity score adjusted analysis by means of inverse probability of treatment weighted Cox regression was also performed. Propensity scores were the standardized individual probabilities of being on-LMWH estimated by logistic regression that considered baseline covariates as independent variables.

Laboratory tests at the time of the index endoscopy were available in 177 patients, 73 on-LMWH (91.2%) and 104 no-LMWH (56.2%); 6 bleeders (100%) and 171 non-bleeders (66.1%).

RESULTS

In the accrual period, 27,204 upper endoscopies were performed and a total of 686 EVLs (2.5%) on 379 patients were counted. Hundred and fourteen patients were excluded according to selection criteria. The majority of excluded patients had not well characterized varices for bloody endoscopic field at index endoscopy (N = 55) and TIPS placement during initial follow up (N = 29) (Figure 1B). Among the 114 excluded patients there were 4 patients on vitamin K antagonist (VKA) and 3 on LMWH, whose anticoagulant treatment was withdrawn after the first EVL.

Two hundred sixty-five patients, who received 553 EVLs, were ultimately eligible for the study. Of these, 215 (81.1%) underwent EVL as a primary prophylaxis.

Basal Clinical Characteristics and Anticoagulation Regimens

The majority of patients were male (70.1%) and their mean age was 61.8 years (median 63 years, range 24-85 years). HCV was the most frequent etiology (40.8%) followed by alcohol (15.5%). Forty-seven patients presented with a history of HCC

(17.7%).

Eighty patients (30.1%) were maintained on LMWH during the entire period of eradication treatment (on-LMWH group) and underwent a total of 169 EVL sessions (30.5%). The remaining 185 patients (69.9%) did not receive any anticoagulants (no-LMWH group) and underwent 384 EVL sessions (69.5%).

No differences in demographic and etiologic variables were appreciated between the study groups (Table 1). Biochemical tests were similar with the exception of INR that was slightly lower in on-LMWH (1.25 ± 0.17 vs. 1.34 ± 0.22; p = 0.001). Prognostic scores of liver disease were similar. Basal HVPG according to selected criteria was performed in 119 patients, 28 on-LMWH (35%) and 91 no-LMWH (49.1%). HVPG levels were similar between groups.

Main indications for anticoagulation within the on-LMWH was PVT (80%) (Table 1). Twenty-eight patients (35%) received a subcoagulant regimen (70 U/Kg bid), while the remaining 52 (65%) were treated with a full anticoagulation (100 U/Kg bid) (Supplementary Table 1). The subcoagulant regimen in the peri-procedural period was indicated in patients enrolled before year 2012. Among these there were 12 patients primarily on the VKA warfarin at first EVL, whose INR, between 2 and 3 before the shift to LMWH, was normalized by oral treatment with vitamin K soon after the shift. None of the patients reintroduced VKA during the entire eradication period (that is, all of them were maintained on anticoagulant dose of LMWH). Eight patients restarted warfarin after control EGDS (median 5 months, range 3-7 months). All of them were completely eradicated.

No patients discontinued the anticoagulant treatment with LMWH throughout the EVL period.

Endoscopic Characteristics at Baseline and Follow-up

Comparison of the endoscopic features at admission showed no differences in size of esophageal varices, presence of red signs, gastric varices, and portal hypertensive gastropathy (PHG) (Table 2). A significant higher proportion of on-LMWH performed EVL as secondary prophylaxis compared to no-LMWH (27.5% vs. 15.1%; $p = 0.025$).

A comparison between groups at the time of the last available endoscopic check is summarized in Table 3. Rates of varices no more suitable of further banding were similar (93.8% vs. 90.8%, $p = 0.479$). Eight patients with persistent large varices after the fourth EVL session underwent late TIPS positioning as secondary prophylaxis of variceal bleeding; 14 more patients either died (6 of these within 4 weeks from index EVL, see below) or underwent liver transplant before achieving eradication. No differences in the number of EVL sessions and in the number of bands used were observed between groups.

GOV-1 were not prophylactically ligated in this cohort.

EVL-related Bleeding

Three on-LMWH (3.75%) and 3 no-LMWH (1.62 %) experienced an episode of esophageal variceal bleeding after EVL, respectively. The 4-week cumulative risk of bleeding was similar between the study groups [p by Log-rank test = 0.291; HR = 2.3, 95%CI = (0.5 - 11.4), $p = 0.305$)] (Figure 2A). Propensity score weighted analysis also gave similar results [HR=1.7, 95%CI = (0.2 - 21.2), $p = 0.662$]. As expected, no bleeding episodes were observed after the second week post-EVL (Figure 2A). Two patients bled after the first EVL session, two after the second, one after the third, and the last after the fourth EVL session. The 3 on-LMWH bleeders

were on anticoagulant dose of LMWH at the moment of the hemorrhage. Table 4 summarizes the characteristics of the bleeders (N=6) vs. the non-bleeders (N=260). Main clinical and biochemical parameters, including traditional coagulation tests and prognostic scores for liver disease, were similar between the two groups except for mean serum creatinine, that was significantly higher in bleeders (Table 4). This higher value was determined by two bleeders, who presented with kidney failure (one of this, a no-LMWH patient, died 6 hours after the bleeding episode as reported in Supplementary Materials). PVT was present in the majority of bleeders (N=4, 66.7%) (Table 4). Three of these patients were on LMWH for occluding thrombosis since the first EVL, while the remaining was diagnosed with non-occluding thrombosis of the splenic vein after the post-EVL bleeding episode (no-LMWH patient). All bleeders showed large varices with red signs at the index EVL and received a significantly higher number of bands than non-bleeders (Table 4).

No further bleeding episodes (neither gastrointestinal or in other sites) were registered up to the 3-month control EGDSs.

Survival

Six patients died within 28 days from the last elective banding session, 2 were on-LMWH (2.5%) and 4 (2.2%) were no-LMWH, respectively. Short-term cumulative survival was similar between the study groups [p by Log-rank test 0.863; HR = 1.2, 95%CI = (0.2 - 6.3), p=0.866) (Figure 2 B). Propensity score weighted analysis also gave similar results [HR = 0.9, 95%CI = (0.1-16.6), p = 0.937]. One on-LMWH and 1 no-LMWH died 48 and 6 hours after a post-EVL bleeding episode (their medical history is described in Supplementary Results). Two more no-LMWH died for sepsis and one for end stage liver failure. The remaining on-LMWH died because of

hemorrhagic shock following a car accident. Long-term cumulative survival was similar between groups (Supplementary Figure 1).

DISCUSSION

To our knowledge, this is the first study showing that continuous LMWH treatment does not increase the short-term risk of bleeding and death in cirrhotic patients admitted to endoscopic variceal ligation either for primary or secondary prophylaxis of esophageal variceal bleeding. Moreover, only variables indicating the intrinsic risk of bleeding from varices (i.e., their size) and, consequently, the higher number of bands used for their obliteration appeared to be significantly linked to endoscopy proven hemorrhages. The presented rate of bleeding after EVL was in line with that reported in cirrhotic patients without both portal vein thrombosis and anticoagulation treatment [12, 13]. While clear data connecting the coagulative status of cirrhotic patients and their risk of bleeding have never been consistently provided [29], variceal bleeding has been related to the level of portal hypertension [30] and to the endoscopic characteristics of varices [21,31]. Our data confirm this evidence and define that there is no apparent causality between post EVL variceal bleeding and anticoagulant treatment [32].

Anticoagulation with LMWH is considered the treatment of choice in the peri-procedural period giving the reported higher risk of bleeding if oral anticoagulants are restarted sooner than 5-10 days after an operative endoscopy [16-20]. However, guidelines are scarcely evidence-based in the setting of prophylactic EVL in cirrhotic patients, being mostly based on expert opinions and small case series [33]. Indeed, timing of AVK withdrawal and imbrication with LMWH has been extrapolated from studies on patients undergoing colonic endoscopic polypectomy [34]. This contributes

to explain the lack of uniformity in the management of anticoagulation in the peri-endoscopic period worldwide [8, 20, 35, 36]. In our study, 12 patients only were under AVK before EVL. In these patients, initial imbrication was strictly applied according to guidelines, including administration of vitamin K [27], but anticoagulant dose of LMWH were maintained thereafter until eradication was achieved (as in patients already on LMWH before EVL).

LMWH has already been shown to be safe in patients with cirrhosis not admitted to invasive procedures [6, 28, 37]. We demonstrate the safety of LMWH also in patients otherwise considered at high risk of bleeding for both the endoscopic procedure (i.e. EVL) and the underlying disease (i.e. cirrhosis further complicated by PVT). Although PVT increases the risk of variceal bleeding in cirrhotic patients [4, 5, 37] and anticoagulation is indicated as its first line treatment [4,5], no clear-cut indication has been provided on the opportunity of performing prophylactic EVL as a concomitant treatment to avoid variceal bleeding [21]. A recent study has shown prophylactic treatment with TIPS as more effective than EVL plus non-selective betablockers and Warfarin for the prevention of rebleeding in patients with non-cavernomatosus PVT [38]. However, in the medical treatment group anticoagulation was administered when eradication was already achieved (14-21 weeks after bleeding) and the post EVL bleeding risk was considered removed. Our results encourage starting PVT treatment with LMWH together with EVL for prophylaxis of esophageal variceal bleeding.

Concordantly with the literature, the majority of bleeding episodes (66.6%) happened during the second week after EVL [11-13] both in on-LMWH and in no-LMWH. Two (one in each group) of the 6 bleeders (33.3%) had kidney failure at the moment of bleeding. Moreover, EVL was not a frequent cause of death (0.7%). The

two patients who died for EVL-related bleeding (one of them on full anticoagulant dose of LMWH after shifting from warfarin) bled early after EVL (48 and 6 hours, respectively). Both of them had extensive thrombosis/cavernoma of portal vein and serious comorbidities (atrial fibrillation/obesity and kidney failure, respectively). We recommend a cautious evaluation of patients with similar characteristics before performing prophylactic EVL.

Main limitation of this study is its retrospective, single center design. Moreover, although the population size was relevant for a single-center study, we had a low number of bleedings and deaths, which caused low statistical power. Furthermore, patients with HCV etiology, low Child-Pugh score and in primary prophylaxis were the majority of the sample. So, further prospective investigations focusing on patients with emerging etiologies, more advanced disease and in secondary prophylaxis are needed.

In conclusion, LMWH does not increase the risk of bleeding and death in cirrhotic patients undergoing prophylactic endoscopic variceal ligation. Overall these data encourage avoiding any interruption or delay of anticoagulation treatment in cirrhotic patients admitted to EVL. These results will require confirmation in randomized trials.

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Table 1: Comparison of baseline clinical characteristics in patients stratified according to anticoagulant treatment.

Variables	**on-LMWH (N=80)**	**no-LMWH (N= 185)**	**p**
Male, N (%)	55 (68.8)	131 (70.4)	.784
Age (years) *	63.5±12.1	61.1±11.5	.138
Etiology, N (%)			
Viral	41 (51.2)	91 (48.9)	
HCV	33 (41.2)	76 (40.9)	
HBV	8 (10)	15 (8.1)	.728
EtOH	8 (10)	35 (18.8)	
NASH	8 (10)	9 (4.8)	

PBC Others	5 (6.3) 18 (22.5)	9 (4.8) 41 (22)	
HCC, N (%)	17 (21.2)	30 (10.8)	.381
Ascites, N (%) Grade 1-2 Grade 3	 5 (6.3) 3 (3.8)	 20 (10.8) 3 (1.6)	.303
HE, N (%)	3 (4.2%)	8 (6.1)	.720
Comorbidities, N (%) Cardiovascular Diabetes Chronic Kidney Disease	 19 (23.8) 20 (25.0) 2 (2.5)	 30 (16.2) 44 (23.8) 4 (2.1)	.455
MAP (mmHg) *	85±10.6	87±12.3	.364
Haemoglobin (g/dl) *	11.5±2.2	11.9±2.05	.227
WBC (10^3/mm^3) *	4.60±2.62	5.10±3.00	.198
Platelets (10^3/mm^3) *	84.1±63.2	88.1±48.2	.630
INR *	1.25±0.17	1.34±0.22	***.001***
Albumin (g/dl) *	3.31±0.72	3.35±0.78	.737
Bilirubin (mg/dl) *	1.53±1.06	1.95±2.55	.172
Creatinine (mg/dl) *	1.04±0.62	1.00±0.81	.707
Child-Pugh score *	6.5±1.5	6.4±1.6	.785
MELD score *	11.2±3.1	12.2±4.7	.053
HVPG (mmHg) *	16.9±8.2°	18.3±5.6°°	.288

On NSBB, N (%)	31 (38.8)	75 (40.5)	.290
On NSBB primarily for Cardiovascular Indications, N (%)	6 (7.5)	12 (6.5)	.675
Started NSBB as Secondary Prophylaxis, N (%)	22 (27.5)	28 (15.1)	***.025***
Started Endoscopic Primary Prophylaxis for HVPG non-response to NSBB, N (%)[@]	3 (3.8)[§]	35 (18.9)	***.001***
Started Endoscopic Secondary Prophylaxis, N (%)	22 (27.5)	28 (15.1)	***.025***
Already on proton pump inhibitors, N (%)	18 (22.5)	35 (18.9)	.507
Started proton pump inhibitors, N (%)	21 (26.2)	43 (23.2)	.640
Anticoagulation Regimen at the time of EVL, N (%)			
Subcoagulant**	28 (35)	-	-
Anticoagulant***	52 (65)		
Indication for LMHW, N (%)			
PVT	64 (80)		
Atrial Fibrillation	7 (8.7)[#]	-	-
Pulmonary Embolism	3 (3.7)[#]		
Deep-vein Thrombosis	5 (6.3)[#]		
Prosthetic Mechanic Heart Valve	1 (1.3)[#]		
PVT features, N (%)			
Portal Trunk	41 (64.1)		
Spleno-portal	7 (10.9)		
Meso-portal	8 (12.5)	-	-
Spleno-mesenteric	8 (12.5)		
Lumen occlusion >50%	39 (60.9)		
Significant vascular recanalization at time of first EVL	9 (14.1)		

*: mean ± SD;

**: 70 U/Kg subcutaneously bid;

***: 100 U/kg subcutaneously bid;

°: 28/80;

°°: 91/185;

#: 12 out of 16 patients without PVT were primarily on VKA;

@: All these patients underwent the first EVL the day after HVPG assessment;

§: All these patients had already shown significant decrease of thrombosis at the moment of hemodynamic evaluation, but they were maintained on LMWH throughout the EVL sessions.

Abbreviations: EtOH, ethanol; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HE, hepatic encephalopathy; H-R, heart rate; HVPG, hepatic venous pressure gradient; INR, international normalized ratio; LMWH, low molecular weight heparin; MAP, mean arterial pressure; NSBB, non-selective beta-blockers; PBC, primary biliary cirrhosis; PVT portal vein thrombosis; VKA, Vitamin K antagonist; WBC, white blood cells.

Table 2: Comparison of baseline endoscopic characteristics in patients stratified according to anticoagulant treatment.

Variables	on-LMWH (N=80)	no-LMWH (N=185)	p
Esophageal Varices, N (%)			
F1	0	0	.860
F1 with red signs	10 (12.5)	11 (5.9)	
F2	11 (13.8)	41 (22)	
F2 with red signs	35 (43.7)	98 (53)	
F3	2 (2.5)	4 (2.2)	
F3 with red signs	22 (27.5)	31 (16.7)	
Gastric Varices, N (%)			
GOV-1	25 (31.3)	45 (24.3)	.791
GOV-1/GOV-2 or IGV-1	4 (5.0)	8 (4.3)	
GOV-2	8 (10.0)	18 (9.7)	
IGV-1	3 (3.8)	9 (4.9)	
PHG, N (%)	70 (87.5)	161 (87)	1.0

Abbreviations: GOV-1, Gastroesophageal Varices type 1; GOV-2, Gastroesophageal Varices type 2; IGV-1, Isolated Gastric Varices Type 1; PHG, portal hypertensive gastropathy.

Table 3: Comparison of endoscopic characteristics at last available EGDS[#] in patients stratified according to anticoagulant treatment.

Variables	on-LMWH (N=80)	no-LMWH (N=185)	p
Esofageal Variceal not suitable of further banding, N (%)	75 (93.8)	168 (90.8)	.479
Esophageal Varices, N (%)			
F1 with red signs	1 (1.3)	1 (0.5)	
F2	3 (3.8)	12 (6.5)	.543
F2 with red signs	1 (1.3)	2 (1.1)	
F3	0	2 (1.1)	
Persistent Large Esophageal Varices	4 (5)	16 (8.6)	.447
Gastric Varices, N (%)			
GOV-1	23 (28.8)	39 (21.1)	
GOV-1/GOV-2 or IGV-1	2 (2.5)	5 (2.7)	.819
GOV-2	8 (10.0)	19 (10.3)	
IGV-1	3 (3.8)	9 (4.9)	
PHG, N (%)	65 (81.3)	163 (88.1)	.139
Mean EVL Sessions *	2.1±1.2	2.0±1.1	.441
Number of Bands °*	4.7±1.2	4.6±1.1	.756
Total Mean Bands °°*	4.8±1.0	4.7±0.9	.532

[#]: For the majority of patients (75/80 and 168/185 for on-LMWH and no-LMWH, respectively) last available EGDS was the 3-month control endoscopy. For the remaining patients was the procedure before death, liver transplantation and late TIPS positioning.

*: mean ± SD;

°Number of bands used at the last EVL session;

°°Total Mean Bands = (Total number of bands/Total number of EVL

sessions)/Number of Patients.

Abbreviations: EGDS, esophagogastroduodenoscopy; GOV-1, Gastroesophageal Varices type 1; GOV-2, Gastroesophageal Varices type 2; IGV-1, Isolated Gastric Varices Type 1; PHG, portal hypertensive gastropathy.

Table 4: Comparison of clinical and endoscopic characteristics at index EGDS[#] in patients stratified according to post-EVL esophageal varices bleeding.

Variables	Bleeders[@] (N=6)	Non Bleeders[@] (N=259)	p
Age*	47.6±11.3	62.1±11.5	***.003***
Albumin (g/dl) *	3.54±1.03	3.42±0.60	.788
Bilirubin (mg/dl) *	2.21±2.64	1.87±2.27	.720
INR *	1.30±0.22	1.30±0.21	.960
Platelets (10^3/mm^3) *	98.3±58.7	86.8±53.3	.604
Creatinine (mg/dl) *	2.2±2.7**	1.0±0.8	***.001***
Hemoglobin (g/dl) *	11.8±2.3	11.9±1.9	.904
MELD score *	15.1±6.9	11.8±4.1	.056
Child-Pugh score *	6.4±1.6	6.3±1.6	.699
PVT, N (%)	4 (66.7)§	61 (23.6)	***.033***
HCC, N (%)	0 (0)	47 (18.4)	.595
On proton pump inhibitors, N (%)	4 (66.7)	113 (43.6)	.410
Esophageal Varices, N (%)			
F1	0 (0)	19 (7.3)	.289
F1 with red signs	0 (0)	50 (19.3)	
F2	0 (0)	51 (19.7)	
F2 with red signs	2 (33.3)	107 (41.3)	

F3 F3 with red signs	0 (0) 4 (66.7)	6 (2.3) 26 (10)	
Large Varices with red signs, N (%)	6 (100)	133 (51.5)	***.031***
Gastric Varices, N (%) GOV-1 GOV-1/GOV-2 or IGV-1 GOV-2 IGV-1	 2 (33.3) 1 (16.7) 1 (16.7) 0 (0.0)	 60 (23.2) 5 (1.9) 27 (10.4) 12 (4.6)	.329
PHG, N (%)	5 (83.3)	223 (86.1)	.598
Mean EVL Sessions *	2.5±1.1	2.1±1.0	.335
Number of Bands	5.67±0.5	4.6±1.2	***.004***
Total Mean Bands° *	5.4±0.4	4.7±1.0	***.023***
On Endoscopic Secondary Prophylaxis, N (%)	1 (16.7)	49 (18.9)	1.0

[#]: Index EVL was defined as the banding session preceding a) the EGDS demonstrating a bleeding episode; b) the EGDS that showed the absence of varices suitable of further ligation, and c) death, liver transplantation or late TIPS positioning (Figure 1A).

[@]Laboratory tests at the time of the index endoscopy were available in 177 patients, 73 on-LMWH (91.2%) and 104 no-LMWH (56.2%); 6 bleeders (100%) and 171 non-bleeders (66.1%).

*: mean ± SD.

**: creatinine levels higher than the upper limit of normality were detected in 2 out of 6 patients.

°: Total Mean Bands = (Total number of bands/Total number of EVL sessions)/Number of Patients.

§: these patients had a thrombosis demonstrated by imaging at the time of bleeding.

Abbreviations: EGDS, esophagogastroduodenoscopy; GOV-1, Gastroesophageal Varices type 1; GOV-2, Gastroesophageal Varices type 2; IGV-1, Isolated Gastric Varices Type 1; HE, hepatic encephalopathy; HCC, hepatocellular carcinoma; INR, international normalized ratio; PHG, portal hypertensive gastropathy; PVT portal vein thrombosis.

FIGURE LEGENDS

Figure 1

A) Study design. EVLs were performed with an interval of 3-4 weeks. Eradication control was performed about 3 months after the last endoscopic evidence of a successful EVL. B) Cohort of patients included in the study.

Abbreviations: EGDS, esophagogastroduodenoscopy; EVL, endoscopic variceal ligation; HVPG, hepatic venous pressure gradient; LABs, laboratory tests; LMWH, low molecular weight heparin; LT, liver transplant; MELD, Model for End-Stage Liver Disease; TIPS, transjugular intrahepatic porto-systemic shunt.

Figure 2

A) Cumulative risk of short term esophageal variceal bleeding in the study groups. B) Short-term survival of study groups. No patient underwent liver transplantation during the reported follow up.

Abbreviation: LMWH, low molecular weight heparin.

Supplementary Figure 1

Long-term survival of the study groups (follow-up range 0.1-90 months; median 8.47 months). Patients who underwent liver transplantation (n=41) were censored as alive.