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Hemodynamic changes after endoscopic variceal ligation: a cohort study

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ABSTRACT

Background: there is controversy about the need to maintain vasoconstrictor treatment after adequate haemostasis is achieved through endoscopic band ligation (EBL) in bleeding esophageal varices (BEV). Measuring a "before and after urgent-EBL" hepatic venous pressure gradient (HVPG) in acute variceal hemorrhage is very difficult. Thus, the goal of this study was to determine hemodynamic variations after an EBL session. A "before" HVPG (PRE) was performed and another one 24 hours "after-ligation" (POST), in cirrhotic patients undergoing endoscopic band ligation as BEV prophylaxis.

Patients and methods: this was a single-center, cohort, prospective study. Patients followed a program of repeated sessions of EBL until eradication of their varices and underwent a basal hepatic venous pressure gradient (PRE HVPG), without changing their usual treatment with beta-blockers. Subsequently, an endoscopic ligation session was performed, following the clinical practices guidelines. A second pressure

measurement (POST HVPG) was taken 24 hours after the endoscopic treatment.

Results: 30 patients were included. PRE and POST HVPG median results were 16.5 mmHg (14-20) and 19.5 mmHg (17-21), respectively, with a significant increase after the procedure ($p < 0.001$). Percentage variations in portal pressure, based on the baseline gradient values (12, 16 and 20 mmHg), were higher for patients with a lower basal HVPG *versus* a higher HVPG for any of the categories compared ($p = 0.087$, $p = 0.016$ and $p < 0.001$, respectively). In our series, 36.7 % of patients showed a ≥ 20 % gradient increase after ligation.

Conclusion: endoscopic band ligation causes an increase in portal pressure, at least for a transitional period, determined by the hepatic venous pressure gradient.

Keywords: Bleeding esophageal varices. Portal hypertension. Venous pressure gradient.Endoscopic band ligation. Secondary prophylaxis.

INTRODUCTION

Patients with chronic liver disease and portal hypertension may present bleeding esophageal varices, when the hepatic venous pressure gradient (HVPG) exceeds 12 mmHg (1-3). The measurement of HVPG in cirrhotic patients provides useful prognostic information on the evolution of the bleeding episode and long-term survival.

Recent studies (4-8) have raised controversy about need to maintain vasoconstrictor treatment after achieving an adequate haemostasis through endoscopic band ligation (EBL) in acute bleeding esophageal varices (BEV). *A priori,* the hypothesis of this study was that there is an increase in portal pressure after ligation, at least transient, which would argue in favor of maintaining vasoconstrictors after emergency endoscopic therapy. The measurement of "emergency pre-ligation" HVPG in acute bleeding varices is difficult (9). Therefore, the main objective of the study was to determine the portal pressure variations after an EBL session, by "pre" HVPG and "post-EBL" measurements 24 hours later in cirrhotic patients undergoing endoscopic band ligation as BEV prophylaxis. The secondary objectives were: a) determine post-ligation portal pressure variations, with respect to a baseline gradient threshold and estimate the percentage of patients with an HVPG increase ≥ 20 %; and b) assess the relationship

between HVPG and the endoscopic aspect of esophageal varices (EV) for patients incl uded in an eradication protocol with EBL.

PATIENTS AND METHODS

This was a single-center, prospective, cohort study, performed at the Bleeding Unit of the Digestive Diseases Department of Hospital Universitario La Paz, between January and December, 2018. Patients were considered eligible for the study if they had cirrhosis, included in an endoscopic eradication program for BEV prophylaxis with an EBL history during the previous 12 months and required a new band ligation session. Cirrhotic patients in the eradication program, with a time interval in excess of 1 year from the last ligation and patients with portal thrombosis, pre-hepatic portal hypertension and hepatocellular carcinoma in B and C stages (according to the BCLC classification) were excluded. All patients signed an informed consent form, after receiving detailed information on the procedures and the purpose of the study. The protocol was approved by the Clinical Research Ethics Committee of the Hospital Universitario La Paz (HULP Code: PI-3068).

Methods

All patients in the endoscopic eradication program, except for those with exclusion criteria, underwent a baseline hepatic venous pressure gradient evaluation (PRE HVPG) without modifying their usual β-blockers treatment. An endoscopy was subsequently performed for a potential variceal band ligation, with no prior knowledge of their hepatic manometry, following clinical practices guidelines (1,2). Patients that required endoscopic ligation were included in the study and underwent a second pressure measurement (POST HVPG) 24 hours later, in order to confirm any portal pressure changes. Their usual β-blocker treatment was maintained (Fig. 1). In order to minimize the discomfort of patients undergoing two HVPG measurements in a short time period, the right internal jugular vein cannulation was maintained from the first procedure, to facilitate measuring the second gradient without having to perform another vein access. Patients were only included once, even when requiring a new band ligation session during the year of the study.

The hepatic pressure gradient was determined in accordance with the standard international recommendations (10,11), by two expert radiologists of Intervention Radiology Unit of the Hospital Universitario La Paz. The right jugular vein was catheterized under local anesthesia, a 8-10 Fr venous introducer was placed using Seldinger's technique and the catheter was advanced under fluoroscopic control into the inferior vena cava and right hepatic vein. The free hepatic venous pressure (FHVP) was measured by maintaining the tip of the catheter "free" in the hepatic vein, at 2 to 4 cm from its opening into the inferior vena cava. The FHVP should be close to the inferior vena cava pressure, the difference between both values is lower than 1-2 mmHg. Wedged hepatic venous pressure (WHVP) was measured by occluding the hepatic vein and inflating a balloon at the tip of the catheter. All measurements were taken in triplicate and the final value was calculated as the mean of these measurements.

Endoscopy was performed at the Bleeding Unit of the Hospital Universitario La Paz, under anesthetic sedation. The endoscopes used were Olympus (GIF-H180, GIF-H190) and the elastic band system used was the Speedband Superview Super7 Multiple Band Ligator (Boston Scientific). Esophageal varices are classified as small and large (12,13), identifying red wale marks as a sign of bleeding risk. EBL was prescribed, following clinical practice guidelines, for large varices or small varices with red wale marks and/or Child's C stage as primary prophylaxis and until the complete variceal eradication in secondary prophylaxis.

Sample size

Sample size was determined based on the number of patients that complied with the inclusion criteria in the reference hospital area (population: 505,644) during the 12 month study period. Based on the results obtained, this 30-patient sample can detect a difference in HVPG ≥ 2.4 mmHg (assuming a 3.1 mmHg standard deviation of the differences) with a confidence interval of 99 % and 95 % power.

Statistical analysis

The SPSS 24.0 software was used for statistical analysis and $p < 0.05$ (bilateral) was considered as statistically significant. Qualitative variables were expressed as

frequencies and percentages while quantitative variables were expressed as the mean (SD), range (minimum-maximum) and median (25 percentile -75 percentile).

Differences in the qualitative variables percentage distribution were reviewed using the Chi-square test or Fisher's exact test, where applicable. Normality testing of continuous variables was assessed using the Kolmogorov-Smirnov test with Lilliefords correction. The corresponding parametric or nonparametric tests were applied, t-Student or Mann-Whitney for inter-group analysis and t-Student for paired samples and Wilcoxon for paired samples in the intra-group analysis.

RESULTS

Thirty cirrhotic patients in an EBL program as prophylaxis for BEV that required a new ligation session were included in the study (Fig. 2). Table 1 shows demographic, liver disease and BEV prophylaxis characteristics for the patient cohort. All patients underwent a baseline hepatic vein pressure gradient (PRE HVPG) with a median of 16.5 mmHg (P25: 14, P75: 20). The 86.7 % (26) had a ≥ 12 mmHg gradient, 56.7 % (17) ≥ 16 mmHg and 30 % (9) ≥ 20 mmHg. Four patients (13.3 %) had a gradient lower than 12 mmHg. After performing an EBL session (median: 3 bands, P25: 2 and P75: 4), a second gradient measurement was performed 24 hours after the endoscopic therapy (HVPG POST) (Fig. 3), with a median of 19.5 mmHg (P25: 17 and P75: 21).

Values for both baseline and 24-hour gradients determined that the median of the differences (POST HVPG - PRE HVPG) was +2 mmHg, reflecting the absolute pressure change after ligation. This increase becomes even more evident when we consider the percentage post-pre change in the gradient (median: 14.6 %; P25: 0, P75: 31.3), showing that the HVPG POST gradient increased by at least 14.6 % with respect to the baseline measurement (PRE) for 50 % of the patients and the change was less than 14.6 % for the remaining patients. When analyzing by sub-groups based on the baseline gradient, the percentage increase in the gradient induced by EBL is higher in patients with lower PRE HVPG (Table 2). Thus, for the PRE HVPG < 12 mmHg patient group, the median of the post-pre gradient percentage change was 40.3 % and 14.3 % for the PRE HVPG ≥ 12 mmHg group, almost reaching statistical significance ($p = 0.087$). Likewise, the median of the gradient percentage changes for HVPG < 16 and ≥ 16 mmHg groups were 21.4 % and 0.00 %, respectively ($p = 0.016$). For HVPG < and ≥

20 mmHg, the percentages were 21.4 % and -4.3 %, respectively (p < 0.001). In our series, 36.7 % of the patients had a gradient increase of ≥ 20 % after ligation (Table 3) and was null for PRE HVPG ≥ 20 mmHg patients *versus* 52.4 % with a ≥ 20 % increase observed in PRE HVPG < 20 mmHg patients (p = 0.011).

Regarding endoscopy, 25 patients had large varices (83.3 %) and 5 small varices (16.6 %), with red wale marks in 21 cases (70 %). Significant differences were observed in the percentage of patients with HVPG < 12 and ≥ 12 mmHg according to the size of varices. Ninety-six per cent of patients with large varices had a PRE HVPG ≥ 12 mmHg, *versus* 40 % in patients with small varices (p = 0.009). The median PRE gradient was also significantly higher for patients with large varices *versus* those with smaller ones (17.0 *vs.* 9.0 mmHg, respectively; p = 0.019). No significant differences were found between different gradient values and red wale marks. With regard to patients with HVPG < 12, 75 % did not have any red wale marks while 25 % had red wale marks. Whereas, with regard to the group with HVPG ≥ 12, 23.1 % did not have these risk signs and 76.9 % had them (p = 0.069). The median of EBL sessions before the endoscopy in this study was 3 (P25: 1, P75: 6).

DISCUSSION

Our study demonstrates that endoscopic variceal ligation produces a significant increase in the hepatic vein pressure gradient (PRE-EBL median: 16.5 mmHg *vs.* POST-EBL median; 19.5 mmHg), at least during the first 24 hours after the procedure. This translates into an increase in portal pressure. The main characteristics of the cohort in this study were: a) all patients had cirrhosis with a history of endoscopic ligation during the previous 12 months as prophylaxis of variceal bleeding, whether due to prior BEV (93.3 %) or for primary prophylaxis for large varices with intolerance to beta-blockers (6.7 %); and b) 90 % were treated with beta-blockers, which were maintained throughout the study period. Both circumstances can explain some of the differences with respect to the baseline gradient values reported in other studies (14-16).

In 1997, Sato (17) demonstrated an increase in portal flow after EBL with Doppler ultrasound and since then, only a few published studies have determined any changes in portal pressure after the endoscopic therapy via hepatic manometry. Li et al. (18) showed an inverse relationship between HVPG and complete EV eradication rates

through EBL, in *in vitro* porcine models.

Avgerinos et al. (15) performed a study of 25 patients with acute BEV treated with ligation and 25 with sclerotherapy. After EBL, a significant increase in HVPG was observed that was maintained for 24 hours, which is similar to our findings. They also observed a continuous reduction in pre-treatment values for the next 48, 72, 96 and 120 hours after the ligation. Nevertheless, patients treated with sclerotherapy showed a greater increase in pressure that was maintained over time (> 120 h), resulting in a higher rebleeding risk *versus* the ligation group.

Until now, no other study had analyzed gradient variations with respect to their baseline figures (HVPG PRE). Our analysis demonstrates that the percentage gradient increase induced by EBL is much higher, the lower the HVPG PRE. Thus, the increase in pressure observed after ligation is proportionally greater in patients with lower baseline gradient values. It is less marked in those with a higher PRE GPVH ≥ 20 mmHg; even when a decrease was observed GPVH POST with regard to the baseline determination.

Lo et al. (14) observed an increase in portal pressure via direct portal vein puncture in 68 % of patients and a reduction in 32 % of the 25 patients that underwent eradication with EBL. The decrease demonstrated was “potentially” attributed to the existence of additional conditions, such as other than esophageal veins, which would enable the “discharge” of excess pressure. However, this was that was not evaluated in our patients.

On the other hand, patients are considered to respond to beta-blockers (19,20) when HVPG < 12 mmHg is achieved (total response) or when their HVPG reduces by more than 20 % with respect to baseline figures in secondary prophylaxis or by more than 10 % in primary prophylaxis (partial response). Based on this circumstance, it can be inferred that a gradient elevation of ≥ 20 % would increase the chances of bleeding, at least theoretically. In our series, 36.7 % of patients had a gradient increase of ≥ 20 % after ligation. In fact, there was virtually no effect in patients with HVPG PRE ≥ 20 mmHg compared to 52.4 % with an increase of ≥ 20 %, which was observed in patients with HVPG PRE < 20 mmHg ($p = 0.011$).

Regarding the endoscopic findings and their relationship with the GPVH PRE, there was a limitation posed by the post-ligation consequences of distorting the endoscopic

aspect of varices by minimizing their appearance. However, our study showed significant differences in the percentage of patients with a gradient < 12 mmHg and ≥ 12 mmHg depending on the size of their varices.

The median of the PRE gradient was significantly higher in patients with large varices compared to those with smaller ones (17.0 *vs.* 9.0 mmHg, respectively; p = 0.019). Even though there was an endoscopic alteration typical of a "treated esophagus", with a median of 3 previous ligation sessions and similar behavior to untreated varices. A gradient ≥ 12 mmHg was also evident in 96 % of patients with large varices *versus* 40 % observed in those with small ones (p = 0.009).

Our study demonstrates that esophageal varices endoscopic ligation induces an increase in portal vein pressure, at least transient, determined by hepatic venous pressure gradient. The increase in pressure (both, absolute and relative) will be higher the lower the baseline gradient. This reinforces the recommendations of the current guidelines, which recommend to maintain the vasoconstrictor treatment in acute variceal bleeding after achieving an adequate haemostasis via endoscopic band ligation.

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Table 1. Demographic, clinical and prophylaxis characteristics. Hepatic venous pressure gradient (HVPG) before (PRE) and after (POST) endoscopic band ligation (EBL)

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n	30
Sex; n males (%)	24 (80 %)
Age [years; mean, ± SD]	58.8 (± 9.8)
Child Pugh n (%)	29 (96.7 %)
Child Pugh A; n (%)	20 (69.0 %)
Child Pugh B; n (%)	8 (27.6 %)
Child Pugh C; n (%)	1 (3.4 %)
MELD [median (p25-p75)]	9,0 (8.0-11.0)
Etiology n (%)	30 (100 %)
Alcohol; n (%)	12 (40 %)
Virus; n (%)	10(30 %)
Mixed (alcohol + virus); n (%)	3 (10 %)
Non-alcoholic steatohepatitis; n (%)	3 (10 %)
Other; n (%)	3 (10 %)
BEV prophylaxis	
Primary; n (%)	2 (6.7 %)
Secondary; n (%)	28 (93.3 %)
β-blockers treatment; n (%)	27 (90 %)
EBL; n (%)	30 (100 %)
NO. elastic bands [n; median (P25-P75)]	3 (2-4)
Previous sessions bands [n; median (P25-P75)]	3 (1-6)
HVPG pre EBL [mmHg; median (P25-P75)]	16.5 (14.0-20.0)
HVPG post LEB [mmHg; median (P25-P75)]	19.5 (17.0-21.0)

MELD: Model for End-stage Liver Disease.

Table 2. Absolute and percentage gradient change after endoscopic ligation, total and with respect to baseline gradient figures

			HVPG absolute change				HVPG percentage change		
		n	**Mean (SD)**	**Median (P25-P75)**	**p(1)**	**p(2)**	**Mean (SD)**	**Median (P25-P75)**	**p(2)**
Total		30	2.4 (3.0)	2.0 (0.0-5.0)	*< 0.001*	---	19.1 (24.0)	14.6 (0.0- 31.3)	---
HVPG PRE	< 12	4	4.0 (3.2)	3.5 (1.5-6.5)	0.068	0.340	45.1 (34.6)	40.3 (18.1-72.2)	0.087
HVPG PRE	≥ 12	26	2.2 (3.0)	2.0 (0.0-5.0)	*0.002*		15.2 (20.0)	14.3 (0.0-29.4)	
HVPG PRE	< 16	13	3.7 (2.8)	2.0 (2.0-6.0)	*0.002*	0.073	32.3 (26.2)	21.4 (14.3-46.7)	*0.016*
HVPG PRE	≥ 16	17	1.5 (3.0)	0.0 (-1.0-3.0)	*0.045*		9.1 (16.8)	0.0 (-4.3-17.6)	
HVPG PRE	< 20	21	3.6 (2.6)	3.0 (2.0-6.0)	*< 0.001*	*0.001*	28.0 (22.8)	21.4 (14.3-37.5)	*< 0.001*
HVPG PRE	≥ 20	9	-0.3 (2.1)	-1.0 (-2.0-0.0)	0.733		-1.6 (9.8)	-4.3 (-9.1-0.0)	

(1) Comparison HVPG PRE – HVPG POST intra-groups (paired samples).

(2) Comparison absolute/percentage HVPG change between groups.

Table 3. Gradient increase ≥ 20 % after endoscopic ligation, with respect to baseline gradient figures

HVPG increase	**Total**		**HVPG PRE**											
	< 12		**≥ 12**		**< 16**		**≥ 16**		**< 20**		**≥ 20**			
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
< 20 %	19	63.3	1	25.0	18	69.2	6	46.2	13	76.5	10	47.6	9	100.0
≥ 20 %	11	36.7	3	75.0	8	30.8	7	53.8	4	23.5	11	52.4	0	0.0
			p = 0.126				p = 0.132				*p = 0.011*			

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Fig. 1. Procedures timeline.

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Fig. 2. Flowchart, population included and excluded in the analysis.

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Fig. 3. PRE and POST LBE individual changes of the hepatic venous pressure gradient.