ANNALS of Hepatology

ORIGINAL ARTICLE

January-March, Vol. 9 No.1, 2010: 15-22

Endoscopic band ligation *versus* propranolol for the primary prophylaxis of variceal bleeding in cirrhotic patients with high risk esophageal varices

Rosa María Pérez-Ayuso,* Sebastián Valderrama,† Manuel Espinoza‡,§ Antonio Rollán,|| René Sánchez,¶ Francisco Otarola,† Brenda Medina,† Arnoldo Riquelme*

*Department of Gastroenterology. † Department of Internal Medicine. ‡ Department of Public Health, Facultad de Medicina Pontificia Universidad Católica de Chile, Santiago, Chile
§ Hospital de Urgencias Asistencia Pública
|| Department of Gastoenterology, Latin-American Endoscopic Training Center, Facultad de Medicina, Universidad del Desarrollo – Clínica Alemana, Santiago, Chile.
¶ Department of Gastroenterology and Endoscopy Unit, Hospital Dr. Sótero del Río

ABSTRACT

Background. Gastroesophageal variceal bleeding is a common complication of portal hypertension. Current guidelines recommend β-blockers for primary prophylaxis. However, evidence suggests that endoscopic variceal ligation (EVL) reduce bleeding episodes. **Aims.** To compare endoscopic EVL with propranolol (PPL) for primary prophylaxis of variceal bleeding. **Methods.** We conducted a randomized controlled trial. Over a 9-year period, 75 patients with cirrhosis and high-risk esophageal varices (HREV) were recruited and allocated to EVL (n=39) or PPL (n=36). Primary outcome was variceal bleeding. Secondary outcomes were survival, source of bleeding and serious adverse events. Analyses were made by intention-to-treat. **Results.** Baseline characteristics were similar. Medium follow-up was 1647±1096 days. Complete follow-up was achieved in 85% of patients. Variceal bleeding occurred in 12% of EVL and in 25% of PPL group (p=0.17). The actuarial risks of bleeding after 2 years were similar in both groups. Overall mortality was 51% in EVL and 33% in PPL group (p=0.17). Patients in the EVL group showed a lower rate of esophageal variceal bleeding (5.1% v/s 25%, p=0.027) and a higher rate of subcardial variceal bleeding compared with PPL group (7.7% v/s 0%, p=0.027). Serious adverse events related to EVL occurred in 2 patients, including 1 death. **Conclusions.** The present study supports that PPL should be considered the first choice in primary prophylaxis of variceal bleeding offering similar effects and lower severe adverse events compared with EVL.

Key words. Primary prophylaxis. Endoscopic band ligation. Propranolol. Beta-Blockers. Variceal bleeding. Cirrhosis. Randomized Controlled Trial.

INTRODUCTION

About 50% of patients with cirrhosis develop gastroesophageal varices. Their presence correlates with the severity of liver disease.[1] Variceal bleeding is a frequent and important complication of portal hypertension. It occurs in 30-40% of cirrhotic patients,[2] with a mortality rate up to 30% for initial bleeding episodes[3,4] and more for recurrences. Prophylactic treatment prior to the first bleeding is mandatory and is currently recommended for high risk patients.[5,6] Non selective β-blockers are currently the first-line agents of choice, reducing bleeding incidence and bleeding related mortality.[7] However, pharmacotherapy with β-blockers is not optimal: 30% to 40% of patients will not achieve a sufficient reduction of portal pressure to prevent bleeding,[8-10] 15-20% will have contraindications to β-blockers and 25-30% will experience side-effects.[11,12] Therefore, therapeutic alternatives to β-blockers are needed.

Because of its efficacy and safety, endoscopic variceal ligation (EVL) has become the method of choice

Correspondence to the author: Rosa María Pérez-Ayuso MD.
Department of Gastroenterology
Pontifica Universidad Católica de Chile
Marcoleta 367, Santiago
Casilla 114-D
Telephone/Fax number: 56-2-3543820 / 56-2-6397780
E-mail: rperez@med.puc.cl

Manuscript received:October 14, 2009.
Manuscripr accepted:October 29, 2009.

for secondary prophylaxis of variceal bleeding.[13,14] As a result of this favourable experience, there has been interest in extending use of EVL to the primary prophylaxis of oesophageal variceal bleeding. To date several randomized-controlled trials (RCT)[15-22] comparing EVL with standard treatment (β-blockers) have been published with conflicting results. Shepke at al. [16] and Lui et al.[20] reported similar results in patients with high-risk varices, while others reported significant higher rates of failure, first variceal bleeding [18,19] and mortality [19] with propranolol (PPL).

The purpose of this study was to perform a RCT comparing EVL with PPL for primary prevention of variceal bleeding in high risk patients. Outcomes included variceal bleeding, survival, source of bleeding and serious adverse events.

PATIENTS AND METHODS

Patients

Cirrhotic patients presenting from April 1998 to June 2007 were screened in 2 tertiary care referral medical centers. Eligible patients included:

a) Cirrhosis diagnosed on the basis of clinical, biochemical, histologic or ultrasonographic evidence.
b) No history of hemorrhage from esophageal varices.
c) High risk varices, defined as large size or medium sized (diameter between 3 and 5 mm) with red color signs.[2]
d) No current treatment with β-blockers.

Patients were excluded if they were younger than 18 or older than 70 years, had big gastric varices, evidence of portal thrombosis, malignancy including hepatocellular carcinoma, contraindication to β-blockers (chronic obstructive pulmonary disease, type 1 diabetes mellitus, congestive heart failure, asthma, complete atrioventricular block), previous variceal endoscopic treatment, transjugular intrahepatic porto-sistemic shunt, surgical shunt, renal failure (creatinine >2.0 mg/dL) or denial to participate in the study.

The severity of liver disease was classified according to Child-Pugh score. The etiology of cirrhosis was divided in alcoholic, viral and others. The study was performed according to the 1975 Declaration of Helsinki. The study protocol was approved by the ethics committees of participating centers. Written informed consent for was asked to the patient or their families.

Randomization

Patients were randomly assigned to pharmacological or endoscopic therapy. Stratified randomization was centrally performed according to Child-Pugh classification (Child-Pugh-Score < 9 or ≥9). Random allocation sequence was generated using numerated sealed envelopes. After the randomization the patient and physicians were informed.

Pharmacological treatment

Propranolol was started at a dose of 20 mg twice daily. Dosage was increased every 3 days until a reduction of 25% of the pre-treatment resting heart rate was achieved, the heart rate was 55 beats per minute or systolic blood pressure was <90 mm Hg. The maximum dose accepted was 320 mg/day. Afterwards, the dosage was adjusted in each clinical control according the resting heart rate. Patients having severe side effects were instructed to report to study investigators and a crossover to EVL was allowed with intention-to-treat analysis. Adherence was assessed by pill counting.

Endoscopic treatment

Variceal ligations were performed at 3 weeks intervals until eradication. Successful variceal eradication was defined as the absence of ligable esophageal varices. During each session, up to 6 bands were placed beginning in the distal esophagus using a multiband ligation device (Sixshooter; Wilson-Cook Inc., Winston-Salem, NC or Speedband; Boston Scientific, Inc., Natick, MA). Overtube or other band ligation devices were not used. Minor adverse events included gastrointestinal discomfort (retroesternal pain or dysphagia). Severe side events include gastrointestinal bleeding and death following the procedure. After variceal eradication, endoscopic control was scheduled every 3 month. Religation was performed when at least 1 varix with a diameter greater than 5 mm reoccurred and repeated every 3-4 weeks until reobliteration.

Outcomes and clinical evaluation

The primary outcome was gastrointestinal bleeding due to variceal bleeding, according to the Baveno III criteria,[23] which were considered the

updated consensus on definitions, methodology and therapeutic strategies in portal hypertension, when the study was planned. Variceal bleeding was defined as hematemesis and/or melena together with endoscopic signs of bleeding (actively bleeding varix or the presence of a thrombus or a platelet clot on the varix). In cases of hematemesis and/or melena without direct endoscopic signs of variceal bleeding, the absence of other potential bleeding sources after complete upper GI endoscopy and a fall of hemoglobin by 2 g/dL or more were required to fulfill the outcome definition. Bleeding from post-EVL esophageal ulcers was considered as variceal bleeding.

Secondary outcomes included survival, source of bleeding (esophageal, subcardial or gastric varices, portal hypertensive gastropathy, others sources unrelated with portal hypertension) and serious adverse events. Fatal bleeding was defined as any death within 6 weeks after a bleeding episode. An independent committee whose members were unaware of study-group adjudicated the specified end-points. Follow-up visits were performed monthly for the first three months and later every 3 months, and included clinical and laboratory assessment. At each follow-up visit, adverse effects of treatment were assessed. For the PPL group, these were arterial hypotension, dizziness, dyspnea, Raynaud phenomenon or hypoglycemia episodes among patients with diabetes. For the EVL group, these were bleeding, esophageal stenosis, pleural effusions, aspiration, perforation or mediastinitis. Abdominal ultrasound and alpha-fetoprotein were performed every six months. Follow-up endoscopies were performed every 3 months in EVL group and every 6 months in the PPL group.

Other treatments and procedures

Patients who developed clinical gastrointestinal bleeding were hospitalized in ICU, underwent diagnostic and therapeutic endoscopy within 6 hours, most of them received adjuvant vasoactive treatment (octeotride or terlipressin) before or after therapeutic endoscopy and supportive care including blood transfusions. Patients with variceal bleeding that was not controllable by EVL could be treated by any other available therapy (endoscopic sclerotherapy, balloon tamponade, transjugular intrahepatic portosystemic shunt (TIPS), surgical shunting or liver transplantation). Patients who underwent liver transplantation during follow-up were censored.

Statistical analysis

The sample size was estimated based on 17% incidence of variceal bleeding in the group treated with PPL. In addition, 15% of absolute difference between both groups is assumed to be found in a 3 years follow-up. Considering 0.05 of error type I and 80% of power, a sample size of 72 patients per arm was calculated. The recruitment period was extended up to June 2007, in order to achieve the estimated sample size. However, only 75 patients were able to be included for the analysis.

Data were analyzed on an intention-to-treat basis and were expressed as mean (±SD). Differences between groups were analyzed by chi-square test, Fisher exact test, and the unpaired Student t test. The actuarial probabilities of bleeding and death were calculated by using the Kaplan-Meier method, and comparisons were made using the long-rank test. Bleeding episodes prevalence was further compared by chi-square test. A two-tailed p-value of less than 0.05 was considered of statistical significance. Data analysis was performed using STATA 10.

RESULTS

Seventy-five out of 109 patients initially recruited met the inclusion criteria. The main reasons for exclusion were: 11 patients were older than 70 years-old, 1 patient had portal thrombosis, 5 patients had large subcardial varices, 4 patients had hepatocellular carcinoma, 6 patients had contraindications to beta-blockers, 1 patient was unable to receive band ligation, 1 patient had renal failure and 5 patients were uncooperative (unable to give written informed consent or to adhere to follow-up) (Figure 1). Of the 75 patients enrolled, 36 were randomly assigned to PPL group and 39 to EVL group. The most frequent etiology of cirrhosis was alcoholic (18 patients), Non-Alcoholic Fatty Liver Disease (NAFLD) (14 patients), Autoimmune hepatitis (AIH) 10 patients and hepatitis C viral infection (9 patients). Other etiologies included Haemocromatosis 4 patients, Primary Biliary Cirrhosis 3 patients, Hepatitis B viral infection 2 patients and cryptogenic cirrhosis 14 patients.

Patients were followed for a medium of 55 ± 36.5 months (range 0.7 to 119 months). The mean time period between randomization and the end of the study was 67 ± 34.7 months. During the entire follow-up period, 6 patients had to be censored due to liver transplantation. Eleven patients (PPL, 7; EVL, 4) were lost to follow-up. Twenty nine out of

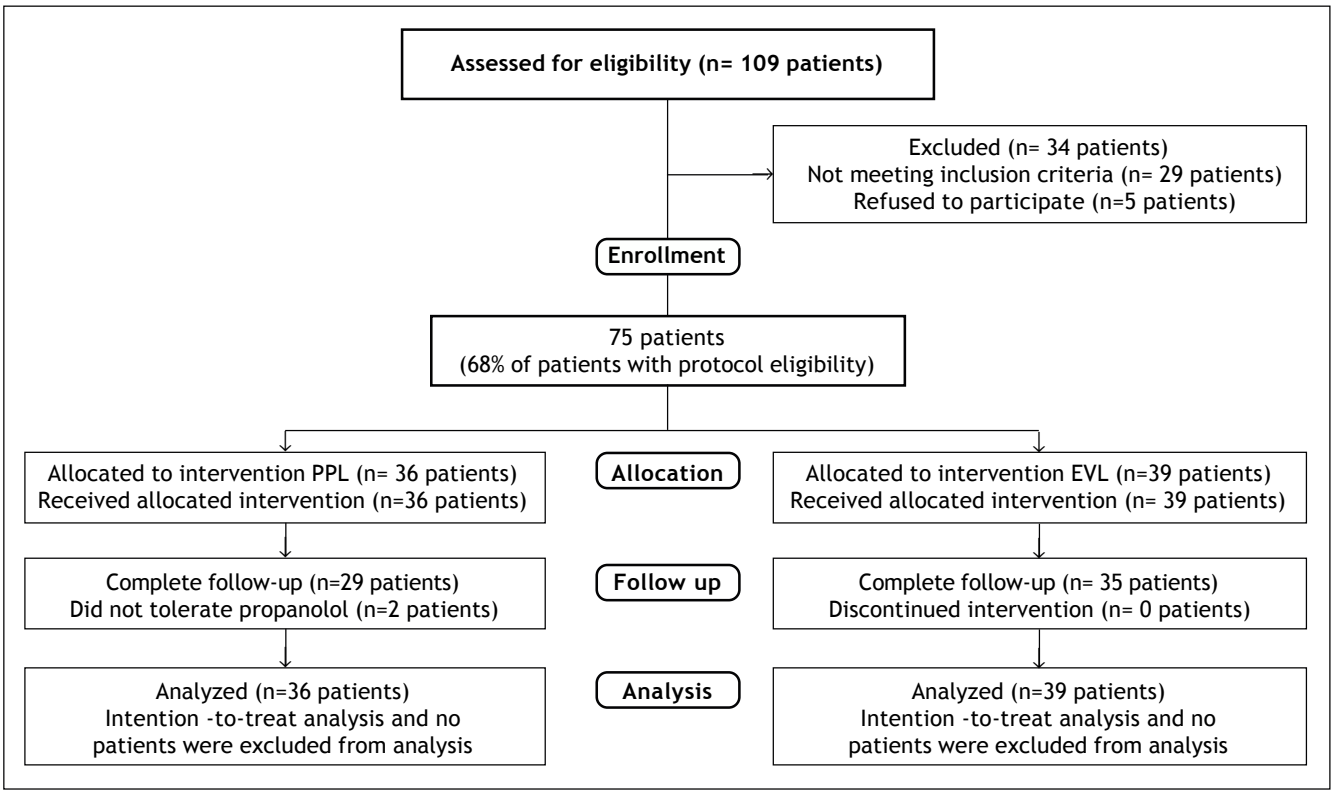

***Figure 1**. Study design and flowchart.*

Table 1. Baseline characteristics.

Variable	Propranolol (n=36)	Endoscopic band ligation (n=39)
Age (years)	58±9	60±7
Sex, n (%)		
Male	18 (50)	19 (48)
Female	18 (50)	20 (52)
Etiology		
Alcoholic cirrhosis, n (%)	10 (27.8)	8 (20.5)
Hepatitis C virus, n (%)	4 (11.1)	5 (12.8)
Others, n (%)	22 (61.1)	26 (66.7)
Child-Pugh class, n (%)		
A	17 (47.2)	23 (59)
B	15 (41.7)	14 (35.9)
C	4 (11.1)	2 (5.1)
MELD	11.5±3.2	10.9±3.6
Ascites, n (%)	14 (38.9)	11 (28.2)
Hepatic Encephalopathy, n (%)	4 (11.1)	4 (10.3)
Bilirubin (mg/dL)	2.2 ± 1.5	2.3 ± 2.4
Albumin (g/L)	3.4±0.64	3.5±0.49
Prothrombin Index (%)	67±20	67±17
Creatinine (mg/dL)	0.9±0.25	0.9±0.18
Subcardial Varices	0	0
Portal hypertensive gastropathy.	13 (36.1%)	17 (43.5%)

36 patients completed the follow-up in the PPL group (81%) and 35 out of 39 patients in the EVL group (90 %) with a p value = 0.26 (Figure 1). Significant differences between the two study groups were not observed in any of the baseline parameters (Table 1).

The mean daily dosage of PPL was 87.5 ± 79.7 mg after titration, according to the protocol. A 25% reduction of resting heart rate was achieved in 86.2% (31/36) of PPL patients. In the EVL group, successful eradication of esophageal varices was achieved in 35/39 (89%). Among the remaining 4 patients, 3 bled before eradication and 1 was lost of follow-up. Variceal eradication required 20.9 ± 9.9 rubber bands placed during 3.2 ± 1.5 endoscopy sessions. Recurrent varices, defined as at least 1 varix with a diameter greater than 5 mm, were observed in 14 out of the 35 eradicated patients (40%). All of them were submitted to new endoscopic ligation without complications.

Adverse events were recorded. In the PPL group 2 patients (5.5%) developed dizziness and dyspnea. PPL had to be withdrawn and a crossover to EVL was made in both patients. In the EVL group 7 patients (17.9%) presented adverse events. In 4 of them the events were considered mild or moderate including dysphagia (2 patients), prolonged odinophagia (1 patient) and esophagitis secondary to biphosphonate therapy (1 patient). Three patients (7.6%) developed serious adverse events (fatal and life-threatening bleeding). Two of them bled from ligation ulcers and 1 patient bled from a subcardial varix during his second EVL, and consequently died from uncontrolled bleeding despite of pharmacological and endoscopic management. These hemorrhagic events were analysed as a variceal bleeding episodes (table 2).

There were no statistically significant differences between the groups with respect to bleeding incidence. During the entire follow-up period, 9 patients (25%) bled in the PPL group and 5 (12.8%) bled in the EVL group (p=0.17; Table 2). However, a significantly higher proportion of esophageal variceal bleeding was observed in the PPL group compared with the EVL group (25% *vs.* 5.1%; p=0.027) (Table 2). Furthermore, in both patients from EVL group that bled from esophageal varices, the event occurred before variceal eradication On the contrary, a significantly higher proportion of subcardial variceal bleeding was observed in the EVL group compared with the PPL group (7.6% *vs.* 0%; p=0.027) (Table 2), even though both groups showed a similar risk of developing subcardial varices or portal hypertensive gastropathy during the follow-up (Table 2).

Bleeding-related deaths occurred in 3 patients (8.3%) in the PPL group compared with 2 patients (5.1 %) in the EVL group (p=0.66; Table 2). Overall mortality, the second primary outcome of the current study, did not differ significantly between the two study groups with 12 (33.3 %) and 20 patients (51.3 %) died in the PPL and EVL group, respectively (p=0.17; Table 2). Mortality risks at 2 years follow-up were 12 (33.3%) for PPL and 19 (48.7%) for EVL. Figure 2 shows the Kaplan-Meier plot of the overall survival curves and there were no statistica-

Table 2. Primary and secondary outcomes

Outcomes	Propranolol (n=36)	Endoscopic variceal ligation (n=39)	P value
Overall bleeding, n (%)	9 (25)	5 (12.8)	NS
Bleeding source, n (%)			
Esophageal varices	9 (25)	2 (5.1)	<0.05
Subcardial varices	0 (0)	3 (7.6)	<0.05
Gastric (fundus) varices	0 (0)	0 (0)	NS
Portal hypertensive gastropathy	0 (0)	0 (0)	NS
Overall mortality, n (%)	12 (33.3)	20 (51.3)	NS
Bleeding related deaths	3 (8.3)	2 (5.1)	NS
Adverse events, n (%)	2 (5.5)	7 (17.9)	NS
Mild events	0 (0)	4 (10)	NS
Severe events	2 (5.5)	3 (7.6)	NS
Incidence of subcardial varices, n (%)	8 (22.2)	6 (15.3)	NS
Appearance or impairment of PHG* n (%)	11 (30)	10 (25.6)	NS

* **PHG:** Portal hypertensive gastropathy.

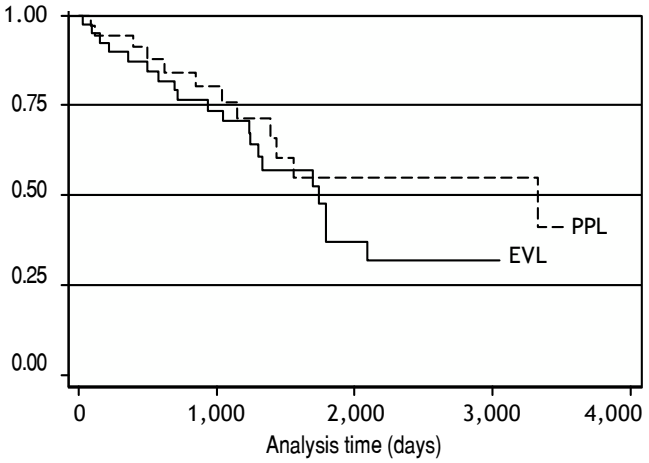

Figure 2. *Kaplan-Meier plot of the overall survival measured in days after randomization.*

lly significant differences between the two study groups (p=0.27, log-rank test).

DISCUSSION

As mentioned, RCT[15-22] comparing EVL with β-blockers for the primary prophylaxis of variceal bleeding in cirrhosis have shown conflicting results. Also, two meta-analysis[24,25] revealed inconclusive results. In the latest, including 596 patients from 8 RCT, the authors concluded that EVL significantly reduced bleeding episodes and had less severe adverse events compared to PPL, but had no effect on mortality.[25]

In agreement with previous studies[15-17,20-22] the present RCT, even showing a tendency towards EVL, did not find significant differences between EVL and PPL with respect to overall or variceal bleeding and overall and bleeding related mortality. This is probably due to a type II error, making these findings questionable. The largest trial to date, from Schepke et al, included only 152 patients.[16] They argue that even though the projected 2 x 200 patients would have been far from sufficient to demonstrate a significant difference in bleeding or mortality rates. To date only 2 trials have shown a significant reduction in bleeding rate in EVL compared with PPL group.[18,19] One of them has been questioned because of an unexplained, higher-than-expected, rate of bleeding in the PPL group.[18] Our study did not show differences between groups, however, the power of the test was only 27.8%. In other words, the probability of no-reject a false null hypothesis (error type 2) was 72.2%. Even though we cannot draw strong conclusions from our study, the data presented can be used for future meta-analysis as the data collected meet quality standards.

In the meta-analysis from Khuroo et al.,[25] the cumulative analysis revealed that the rate of bleeding was not significantly different when first five trials were sequentially added to each other.[18,19,26-28] However, EVL showed a significant reduction in rate of bleeding once the three latest trials[15,16,20] were sequentially added to earlier studies. Subgroup analysis revealed that EVL had significant advantage over β-blockers in trials including ≤30% patients with alcoholic cirrhosis, > 30% patients with Child Class C cirrhosis and > 50 % patients with large varices. In conclusion, this meta-analysis leads to conclude that EVL reduces the rate of first gastrointestinal bleed by 31% compared to β-blockers, with number needed to treat to benefit 1 patient as 15.

One important finding of the present study, which was not reported in previous investigations, is the difference observed with respect to the source of bleeding between groups. Patients from the PPL group showed a significantly higher proportion of esophageal variceal bleeding, while patients from the EVL group showed a significantly higher proportion of subcardial variceal bleeding. Probably, the rather long follow-up period of the study helps to explain the almost 20% overall incidence of subcardial varices that was similar in both groups, and give us the opportunity to make this observation. The higher subcardial variceal bleeding prevalence in the EVL group might be explained by a relatively higher intravariceal pressure in patients from the EVL group with eradicated esophageal varices, compared to patients from PPL group with non-impeded variceal outflow and lower portal pressure. Based on this finding, it is tempting to suggest that combined endoscopic plus pharmacological therapy could reduce even more the risk of first variceal bleeding in patients with cirrhosis compared with PPL or EVL as monotherapy. Currently, there is only one study evaluating the efficacy of EVL plus PPL compared with EVL. Unfortunately, this study carried out by Sarin, *et al*., compared combined therapy *vs*. EVL, which is not considered at the moment the first choice for primary prophylaxis.[29] On the other hand, the follow-up period of this study is not long enough to observe bleeding from subcardial varices, taking into account that 2 out of 3 patients with subcardial variceal bleeding reported in our study bled at 29 and 38 months after the eradication was achieved. In addition, concurrent endoscopic ligation of developing subcardial varices during the follow-up could

also be a good alternative to reduce the risk of bleeding in patients submitted to prophylactic EVL.

Assuming that PPL dosage has been shown to be an important predictor of variceal bleeding risk,[29] in the present study the target heart rate reduction of 25% was achieved in most patients (86.2%), and the mean dose of the β-blocker (87 mg/day) was similar to that reported on previous trials.[16] Only 1 from the 4 patients in whom a 25% reduction of resting heart rate was not achieved bled from esophageal varices. Variceal eradication was also succesfully achieved in most patients in the EVL group (89%). From the 4 patients in which variceal eradication were not achieved, 3 bled before obliteration and were subsequently eradicated as secondary variceal bleeding prophylaxis. As in previous trials, recurrent varices ocurred in 40% of patients during the follow-up and were again submitted to EVL. None of these patients had bled at the end of the study.

The frequency of adverse events was similar between groups, but in the EVL group there were some life-threatening and even fatal complications. Three patients bled during the eradication period and 1 of them died because of an uncontrolable severe hemorrhage from a subcardial varix. However, although side effects in the PPL arm were not fatal, the β-blocker had to be witdrawn in all cases. Although previous studies[18,20] and the meta-analysis from Khuroo, *et al*.[25] showed similar or lower incidence of adverse events in EVL compared with β-blocker group, it is important to remark that they reported all the adverse events while we reported only those with clinical significance. In agreement with our results, the severe adverse events reported in the PPL group in previous trials, even though requiring withdrawal of the drug have never been fatal.

Finally, in the present RCT no significant differences were found between PPL and EVL group with respect to overall and bleeding related mortality. Only 1 trial from Jutabha et al.,[19] has demonstrated significant difference in rate of all-cause deaths between PPL and EVL group, but all the previous controlled studies as well as the latest meta-analysis[25] reported that EVL compared with β-blocker did not affect bleeding related deaths.

In summary, the present study supports that PPL should be the first choice in primary prophylaxis of variceal bleeding offering similar effects and lower severe adverse events compared with EVL. On the other hand, EVL should be offered as primary variceal bleeding prophylaxis in patients with cirrhosis and high risk esophageal varices in whom severe adverse effects or contraindications preclude the use of β-blockers, are non-compliant or who show no adequate haemodynamic response to them. Based on the higher prevalence of subcardial variceal bleeding observed in EVL in comparison with PPL group, we suggest that combined endoscopic plus pharmacological therapy could have a synergic effect. However, the effectiveness of combined prophylactic strategies require further controlled trials.

REFERENCES

1. Pagliaro L, D'Amico G, Pasta L, Politi F, Vizzini G, Traina M, et al. Portal hypertension in cirrhosis: Natural history. In: Bosch J, Groszmann RJ (eds.). Portal Hypertension. Pathophysiology and Treatment. Oxford, UK: Blackwell Scientific; 1994, p. 72-92.
2. The North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. N Engl J Med 1988; 319: 983-9.
3. D'Amico G, de Franchis R. Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. Hepatology 2003; 38: 599-612.
4. Carbonell N, Pauwels A, Serfaty L, Fourdan O, Levy VG, Poupon R. Improved survival after variceal bleeding in patients with cirrhosis over the past two decades. Hepatology 2004; 40: 652-9.
5. Garcia-Tsao, Sanyan A, Grace N, Carey W. Prevention and Management of Gastroesophageal Varices and Variceal Hemorrhage in Cirrhosis. Hepatology 2007; 46: 922-38.
6. de Franchis R. Evolving Consensus in Portal Hypertension Report of the Baveno IV Consensus Workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol 2005; 43: 167-76.
7. D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment ofportal hypertension: an evidence-based approach. Semin Liver Dis 1999; 19: 475-505.
8. Bosch J, Mastai R, Kravetz D, Bruix J, Gaya J, Rigau J, et al. Effects of propranolol on azygos blood flow and hepatic and systemic hemodynamics in cirrhosis. Hepatology 1984; 4: 1200-5.
9. Garcia-Tsao G, Grace ND, Groszmann RJ, Conn HO, Bermann MM, Patrick MJ, et al. Short-term effects of propranolol on portal venous pressure. Hepatology 1986; 6: 101-6.
10. Vorobioff J, Picabea E, Villavicencio R, Puccini V, Rossi O, Bordato J, et al. Acute and chronic hemodynamic effects of propranolol in unselected cirrhotic patients. Hepatology 1987; 7:648-653.
11. Lui HF, Stanley AJ, Forrest EW, Jalan R, Hislop WS, Mills PR, et al. Primary prophylaxis of variceal hemorrhage: a randomized controlled trial comparing band ligation, propranolol, and isosorbide mononitrate. Gastroenterology 2002; 123: 735-44.
12. Abraczinskas D, Ookubo R, Grace N, Groszmann R, Bosch J, Garcia-Tsao G, et al. Propranolol for the prevention of first variceal bleeding: a lifetime commitment? Hepatology 2001; 34: 1096-102.
13. Lo GH, Lai KH, Cheng JS, Chen MH, Huang HC, Hsu PI, et al. Endoscopic variceal ligation plus nadolol and sucralfate compared with ligation alone for the prevention of variceal rebleeding: a prospective, randomized trial. Hepatology 2000; 32: 461-5.

14. De la Pena J, Brullet E, Sanchez-Hernandez E, Rivero M, Vergara M, Martin-Lorente JL, et al. Variceal ligation plus nadolol compared with ligation for prophylaxis of variceal rebleeding: a multicenter trial. Hepatology 2005; 41: 572-8.
15. Lo GH, Chen WC, Chen MH, Lin CP, Lo CC, Hsu PI, et al. Endoscopic ligation vs nadolol in the prevention of first variceal bleeding in patients with cirrhosis. Gastrointest Endosc 2004; 59: 333-8.
16. Schepke M, Kleber G, Nurnberg D, Willert J, Koch L, Veltzke- Schlieker W, et al. Ligation versus propranolol for the primary prophylaxis of variceal bleeding in cirrhosis. Hepatology 2004; 40: 65-72.
17. Song H, Shin JW, Kim HI, Choi J, Lim CY, Kim JW, et al. A prospective randomized trial between the prophylactic endoscopic variceal ligation and propranolol administration for prevention of first bleeding in cirrhotic patients with high risk esophageal varices. J Hepatol 2000; 32: 41A.
18. Sarin SK, Lamba GS, Kumar M, Misra A, Murthy NS. Comparison of endoscopic ligation and propranolol for the primary prevention of variceal bleeding. N Engl J Med 1999; 340: 988-93.
19. Jutabha R, Jensen DM, Martin P, Savides T, Han SH, Gornbein J. Randomized study comparing banding and propranolol to prevent initial variceal hemorrhage in cirrhotics with high-risk esophageal varices. Gastroenterology 2005; 128: 870-81.
20. Lui HF, Stanley AJ, Forrest EH, Jalan R, Hislop WS, Mills PR, et al. Primary prophylaxis of variceal hemorrhage: a randomized controlled trial comparing band ligation, propranolol and isosorbide mononitrate. Gastroenterology 2002; 123: 735-44.
21. Norberto L, Polese L, Cillo U, Grigoletto F, Burroughs A, Neri D, et al. A randomized study comparing ligation with propranolol for primary prophylaxis of variceal bleeding in candidates for liver transplantation. Liver Transpl 2007; 13: 1272-8.
22. De BK, Ghosghal UC, Das T, Santra A, Biswas PK. Endoscopic variceal ligation for primary prophylaxis of esophageal variceal bleed: preliminary report of a randomized controlled trial. J Gastroenterol Hepatol 1999; 14: 220-4.
23. de Franchis R. Updating consensus in portal hypertension: Report of the Baveno III consensus workshop on definitions, methodology and therapeutic strategies in portal hypertension. J Hepatol 2000; 33: 846-52.
24. Garcia-Pagan JC, Bosch J. Endoscopic band ligation in the treatment of portal hypertension. Nat Clin Pract Gastroenterol Hepatol 2005; 2: 526-35.
25. Khuroo MS, Khuroo NS, Farahat KL, Khuroo YS, Sofi AA Dahab ST. Meta-analysis: endoscopic variceal ligation for primary prophylaxis of oesophageal variceal bleeding. Aliment Pharmacol Ther 2005; 21: 347-61.
26. Sarin SK, Guptan RKC, Jain AK, Sundaram KR. A randomized controlled trial of endocopic variceal band ligation for primary prophylaxis of variceal bleeding. Eur J Gastroenterol and Hepatol 1996; 8: 337-42.
27. Chen CY, Sheu MZ, Su SY. Prophylactic endoscopic variceal ligation with multiple band ligator for oesophageal varices. Gastroenterology 1998; 114: A1224.
28. De la Mora JG, Farca-Belsaguy AA, Uribe M, de Hoyos-Garza A. Ligation vs Propranolol for primary prophylaxis of variceal bleeding using multiple band ligator and objective measurements of treatment adequacy: preliminary results. Gastroenterology 2000; 118: A6511.
29. Sarin SK, Wadhawan M, Agarwal SR, Tyagi P, Sharma BC. Endoscopic variceal ligation plus propranolol versus endoscopic variceal ligation alone in primary prophylaxis of variceal bleeding. Am J Gastroenterol 2005; 100: 797-804.
30. Abraldes JG, Tarantino I, Turnes J, García- Pagán JC, Rodés J, Bosch J. Hemodynamic response topharmacological treatment of portal hypertension and long-term prognosis of cirrhosis. Hepatology 2003; 37: 902-8.