TOPIC HIGHLIGHT

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Primary prevention of bleeding from esophageal varices in patients with liver cirrhosis

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Author contributions: Triantos C and Kalafateli M had substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, drafting the article, and final approval of the version to be published.
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Received: November 24, 2013 Revised: February 7, 2014
Accepted: April 11, 2014
Published online: June 27, 2014

Abstract

Variceal bleeding is a life threatening situation with mortality rates of at least 20%. Prophylactic treatment with non-selective beta blockers (NSBBs) is recommended for patients with small varices that have not bled but with increased risk for bleeding. The recommended treatment strategies on primary prevention of variceal bleeding in patients with medium and large-sized varices are NSBBs or endoscopic band ligation. Nitrates, shunt surgery and sclerotherapy are not recommended in this setting. In this review, the most recent data on prevention of esophageal variceal bleeding are presented. Available data derived from randomized-controlled trials suggest both treatment strategies, and according to Baveno V consensus in portal hypertension "the choice of treatment should be based on local resources and expertise, patient preference and characteristics, side-effects and contra-indications".

Key words: Cirrhosis; Portal hypertension; Esophageal varices; Primary prevention; β-Blockers; Endoscopic band ligation

Core tip: The significance of primary prevention of bleeding from esophageal varices in patients with liver cirrhosis is major, considering the high mortality rates that accompany the acute bleeding episode. Current management guidelines suggest the use of either non-selective beta-blockers or endoscopic band ligation with same efficacy between them. In this review, we summarize data from randomized clinical trials or prospective studies together with meta-analytical data, when applicable, to present the most updated recommendations on primary prevention of esophageal variceal bleeding.

Triantos C, Kalafateli M. Primary prevention of bleeding from esophageal varices in patients with liver cirrhosis. _World J Hepatol_ 2014; 6(6): 363-369 Available from: URL: http://www.wjgnet.com/1948-5182/full/v6/i6/363.htm DOI: http://dx.doi.org/10.4254/wjh.v6.i6.363

INTRODUCTION

Bleeding from esophagogastric varices is a life-threatening condition with an incidence of 5%-15% in patients with liver cirrhosis and mortality rates of at least 20%[1,2], despite improvements in the management of these patients. The term pre-primary prophylaxis is used to define the prevention of development and growth of varices. The term primary prophylaxis refers to the prevention of the first variceal bleeding in patients with liver cirrhosis and consists of two main treatment strategies, non-selective beta blockers (NSBBs) aiming to reduce hepatic venous pressure gradient (HVPG) below 12 mmHg or by 20% from baseline levels, and endoscopic band ligation (EBL) performed until variceal eradication[3].

In this review, we discuss the most recent data on primary prevention of variceal bleeding using data from randomized controlled trials (RCTs), prospective studies or meta-analyses focusing mainly on probability of bleeding, mortality and adverse events. We searched MEDLINE

database, Scopus, and ISI Web of Knowledge search system using the textwords "esophageal varices", or "primary prevention of variceal bleeding", or "management of varices" and major Gastroenterology and Liver meetings.

DIAGNOSIS OF VARICES

The esophagogastroduodenoscopy (EGD) is the gold standard for the diagnosis of esophageal varices and should be performed every 2-3 years in patients with compensated cirrhosis and no varices at initial endoscopy, and every 1-2 years in patients with small varices[4]. In patients with decompensated cirrhosis, EGD should be performed yearly[4]. There is a great interest in identifying non-invasive factors to diagnose esophageal varices but currently there is no evidence that their predictive accuracy is equal to that of EGD. Such factors include platelet count, spleen size, portal vein diameter, Child-Pugh score, presence of ascites, albumin levels and transient elastography[5].

In a recent prospective study[6], spleen stiffness (SS) and liver stiffness (LS) were measured by transient elastography in 200 patients with liver cirrhosis of whom 124 (71%) had esophageal varices. There was a significant difference in median LS ($P = 0.001$), SS ($P = 0.001$), LS-spleen diameter to platelet ratio score (LSPS) ($P = 0.001$), and platelet count to spleen diameter ratio (PSR) ($P = 0.001$) between patients with and without esophageal varices. LS $\geq$ 27.3 kPa had a sensitivity of 91%, specificity of 72%, and a diagnostic accuracy of 86% in predicting esophageal varices. LSPS $\geq$ 3.09 had sensitivity and specificity of 89% and 76%, respectively, and a PSR cutoff value of 909 or less had sensitivity of 64%, specificity of 76%, and diagnostic accuracy of 68% in predicting esophageal varices. SS $\geq$ 40.8 kPa had a sensitivity of 94%, specificity of 76%, and diagnostic accuracy of 86% for predicting esophageal varices. SS was significantly higher in patients who had large varices (56 *vs* 49 kPa, $P = 0.001$) and variceal bleeding (58 *vs* 50.2 kPa, $P = 0.001$).

Capsule endoscopy (CE) has been shown to be an accurate prognostic method for diagnosis of esophageal varices but there is no consensus to recommend its use in this setting. In a meta-analysis of 9 studies including 631 patients[7], the pooled sensitivity and specificity of PILL-CAM ESO capsule was 83% and 85%, respectively with positive and negative likelihood ratios of 4.09 and 0.25, respectively. In a recent, prospective study[8], the overall diagnostic yield of CE for esophageal varices was 72% (51 of 71 esophageal varices detected by EGD). The diagnostic yield was significantly greater for F2/F3 esophageal varices than for F1 (87% *vs* 61%, $P = 0.03$) and for varices located at locus superior or locus medialis than those located at locus inferior (85% *vs* 55%, $P = 0.01$). The diagnostic accuracy of CE for gastric varices was low (1 of 29 gastric varices detected by EGD), whereas for portal hypertensive gastropathy was 69% (24 of 35). EGD is superior to CE in grading of esophageal varices because capsule lacks air insufflation.

RISK OF FIRST VARICEAL BLEEDING EPISODE

The major predictive factors of first variceal bleeding episode are the size of varices, the severity of liver dysfunction and the endoscopic presence of red wale marks[9]. However, the combination of these, fails to predict all episodes of bleeding. Thus, new and more accurate predictive factors are needed to predict the first bleeding episode considering the importance to identify the cohort of patients who are mostly in need for prophylactic therapy. A significant factor associated with rupture of varices is an HVPG higher than 12 mmHg[10], considering that a high HVPG relates directly to a high variceal wall tension. Goulis *et al*[11] have proposed that, in patients with large varices and a high wall tension, the release of endotoxin into the systemic circulation during episodes of bacterial infection results in a further increase in portal pressure through the induction of endothelin and possibly vasoconstrictive cyclo-oxygenase products. Furthermore, endotoxin-induced nitric oxide and prostacyclin could inhibit platelet aggregation, thus resulting in variceal rupture. Patients with cirrhosis and bacterial infection demonstrate a heparin effect using heparinase I-modified thromboelastography and have anti-Xa activity[12,13]. A heparin effect was reported immediately after the bleeding episode in patients with liver cirrhosis suggesting a possible association with continued variceal bleeding or early rebleeding[14].

PRE-PRIMARY PROPHYLAXIS

The rate of development of varices in patients with cirrhosis and no varices at initial endoscopy is 8% per year[4] and the strongest predictor for their development is a HVPG higher than 10 mmHg[4]. In a large RCT[15] of 213 patients with cirrhosis and portal hypertension (minimal HVPG of 6 mmHg), the effect of NSBBs (timolol) on the development of esophageal varices or the occurrence of variceal bleeding was assessed (timolol-group, $n = 108$; placebo-group, $n = 105$). During follow-up (mean 54.9 mo), no significant difference was observed between the timolol-group and the placebo-group, regarding development of varices (39% *vs* 40%, respectively; $P = 0.89$). Serious adverse events were more common in the timolol group (18% *vs* 6%, $P = 0.006$). However, the development of varices was less frequent in patients with a baseline HVPG lower than 10 mmHg and in those with a decrease of HVPG $\geq$ 10% at one year. Thus, NSBBs reduce portal pressure; however, they seem to have no effect on the development of varices. According to current evidence, the use of NSBBs in patients with cirrhosis and no varices is not recommended for the prevention of their development[4]. Treatment of the underlying liver disease may decrease portal hypertension and prevent its clinical complications, according to the recent Baveno consensus[3].

Development of large varices in patients with small

varices at initial endoscopy occurs at a rate of 8% per year[4]. The factors associated to the growth of small varices are decompensated liver cirrhosis (Child-Pugh class B or C), alcoholic etiology of cirrhosis and the presence of red wale marks at initial endoscopy[4]. The efficacy of NSBBs on preventing the progression of small to large varices is debated[16,17]. In a randomized double-blind controlled trial[16] aiming to evaluate propranolol in the prevention of the development of large varices in patients with cirrhosis and small or no varices, 102 patients were randomized to receive propranolol (160 mg/d) and 104 to receive a placebo. The proportion of patients with large varices was 31% in the propranolol group and 14% in the placebo group (*P* < 0.05), at 2 years. However, one third of patients were lost to follow-up after 2 years. In a placebo-controlled trial[17], 161 patients with cirrhosis and small esophageal varices were randomized to nadolol (*n* = 83) or placebo (*n* = 78). The dose of nadolol was adjusted to decrease heart rate by 25%. During follow-up (mean: 36 mo), 9 and 29 patients from nadolol and placebo group respectively, developed large varices. At the end of follow-up, the cumulative risk was 20% *vs* 51% (*P* < 0.001). In addition, the cumulative probability of variceal bleeding was lower in the nadolol group (*P* = 0.02), but there was no difference in survival between groups (*P* = 0.33). Treatment withdrawal because of adverse effects was higher in the nadolol group (*P* = 0.01).

According to current treatment guidelines[4], in patients with cirrhosis and small varices that have not bled but with increased risk of bleeding, NSBBs are recommended. In cases of low risk for variceal bleeding, NSBBs can be used, although their long-term benefit has not been well established[4].

PRIMARY PREVENTION OF VARICEAL BLEEDING

Both shunt surgery and sclerotherapy have been abandoned for primary prevention, mainly because of the high incidence of complications[18-21]. According to Baveno V consensus[3], the current treatment strategies for medium/large-sized varices are NSBBs or EBL, which are both effective in decreasing rates of bleeding and mortality. NSBBs are splachnic vasoconstrictors which reduce portal pressure and increase portal resistance through a decrease in portal venous inflow[4]. Endoscopic treatments have no effect on portal circulation as they act locally by obliteration of varices.

NSBBs vs no intervention

Nine randomized clinical trials enrolling 966 patients compared NSBBs with a non-active treatment[22]. The incidence of bleeding was significantly reduced (OR = 0.54, 95%CI: 0.39-0.74), particularly in patients with medium-sized or large varices or in patients with varices and HVPG higher than 12 mmHg. The number needed to treat (NNT) to prevent one bleeding episode was 11. However, only a trend towards reduced mortality was observed (OR = 0.75, 95%CI: 0.57-1.06). In another meta-analysis[23] which analyzed data from four randomized trials (286 patients received b-blockers-propranolol in 203 and nadolol in 83-and 303 patients received placebo), the mean percentage of patients without upper gastrointestinal bleeding after two years was 78% ± 3% in the treatment group and 65% ± 3% in the placebo group (*P* = 0.002), whereas the 2-year survival rate was 71% ± 3% and 68% ± 3%, respectively (*P* = 0.34). The efficacy of b-blockers in the prevention of bleeding or bleeding-related mortality was the same, independently of the cause and severity of cirrhosis, ascites and size of varices. However, when propranolol is discontinued, the risk of variceal hemorrhage returns to what would be expected in an untreated population[24].

The hemodynamic response to treatment with b-blockers is considered appropriate when HVPG is decreased below 12 mmHg or by ≥ 20% of baseline values, 1-3 mo after initiation of treatment. The acute hemodynamic response to b-blockers (20 min after administration of propranolol) was shown useful to predict the long-term risk of first bleeding by reducing HVPG ≥ 10% from baseline values[25,26].

In a recent study[27], patients with esophageal varices with HVPG measurement before and during propranolol treatment were included. HVPG responders were kept on propranolol (PROP group), and non-responders were treated with carvedilol (CARV group). HVPG responders were 36% (37/104), whereas 56% (38/67) non-responders achieved hemodynamic response with carvedilol (the remaining patients were treated with EBL). Carvedilol achieved a greater decrease in HVPG compared to propranolol (-19% ± 10% *vs* -12% ± 11%, respectively, *P* < 0.001). During a 2-year follow-up, bleeding rates were 11%, 5% and 25% for PROP, CARV and EBL, respectively (*P* = 0.0429). Hemodynamic responders showed lower mortality compared to the EBL group patients (PROP 14%/CARV 11% *vs* EBL 31%, *P* = 0.0455). Thus, it seems that carvedilol is more efficient than propranolol to decrease HVPG and it was recently suggested that it might be the beta blocker of choice for portal hypertension[28].

NSBBs have also the potential to protect against spontaneous bacterial peritonitis (SBP) in cirrhotic patients, considering that infection is a risk factor for variceal bleeding[11]. In a meta-analysis of three RCTs and three retrospective studies[29] (including 644 patients, 257 treated with propranolol and 387 receiving no treatment), b-blockers were evaluated against no treatment for the prevention of SBP. There was a statistically significant difference of 12.1% (95%CI: 5.5-18.8; *P* < 0.001) favoring propranolol. The NNT to prevent an additional episode of SBP was 8. In addition, NSBBs can protect against bleeding from portal hypertensive gastropathy by reducing cardiac output and inducing splachnic arterial vasoconstriction[30], whereas endoscopic treatments have no effects on portal inflow or resistance.

However, there are safety issues on the use of NSBBs in patients with cirrhosis and refractory ascites[31,32]. In a

self-control cross-over study[32], 10 patients with cirrhosis and refractory ascites treated with beta-blockers were evaluated regarding the development of paracentesis-induced circulatory dysfunction (PCID defined as an increase in plasma renin concentrations 1 wk after paracentesis). Patients underwent two clinical and biological assessments: first while receiving NSBBs and second after NSBBs discontinuation. Eight patients (80%) treated with NBBs developed PCID whereas only one patient developed PCID after beta-blocker discontinuation. Thus, a RCT comparing EBL and NSBBs in patients with refractory ascites is needed to determine the use of EBL as preferred prophylactic treatment in this subgroup of patients.

EBL vs no intervention

EBL has substituted sclerotherapy and it is the endoscopic procedure of choice in primary prevention. Meta-analysis of eight RCTs[33] showed that EBL is superior to no intervention in reducing both the risk of first variceal bleeding (OR = 0.3, 95%CI: 0.17-0.53) and mortality (OR = 0.42, 95%CI: 0.3-0.6). However, there are safety issues concerning EBL in primary prophylaxis. In a trial by Triantos *et al*[33], EBL *vs* no treatment was compared in cirrhotics with intolerance or contraindications to b-blockers. The trial had to stop prematurely due to increased bleeding. Sixty percent of the bleeding was probably iatrogenic and the authors suggested that EBL might be as harmful as sclerotherapy regarding primary prevention. However, in a prospective cohort study[34], patients with contraindications, intolerance or not responding to beta-blockers who were treated with EBL achieved protection from variceal bleeding comparable to that of good responders to beta-blockers. Furthermore, in another RCT[35,36], which compared EBL (*n* = 75) with propranolol (*n* = 77) for primary prophylaxis in cirrhotic patients with varices > 5 mm, 5 patients (6.7%) bled from ligation ulcers and the treatment-related mortality was 2.6% (*n* = 2/5).

EBL vs NSBBs

A recent meta-analysis[37] included 19 RCTS with 1504 patients (731 treated with EBL and 773 with NSBBs-propranolol in 17 trials, nadolol in one and carvedilol in one). In total, 24% (*n* = 176) randomized to EBL *vs* 23% (*n* = 177) randomized to NSBBs died and meta-analysis showed no difference in mortality between the two treatment groups (RR = 1.09, 95%CI: 0.92-1.30). Upper gastrointestinal bleeding was diagnosed for 14% (*n* = 103) with EBL and 20% (*n* = 158) with NSBBs. EBL appeared to be superior to NSBBs for this outcome (RR = 0.68, 95%CI: 0.52-0.90). EBL also had lower rate of variceal bleeding compared to NSBBs [13% (75/590) *vs* 19% (113/611), RR = 0.66, 95%CI: 0.45-0.96]. However, when analysis included trials with adequate randomization or full papers, EBL showed no superiority to NSBBs for gastrointestinal or variceal bleeding. No difference was seen between the two interventions regarding bleeding-related mortality [5.1% (29/567) *vs* 6.3% (37/585); RR = 0.85, 95%CI: 0.53-1.39]. Treatment with NSBBs was associated with dizziness, hypotension, impotence, lethargy, and peripheral edema, whereas EBL was associated with clinically important bleeding and retrosternal pain.

Combined treatment strategies

Gheorghe *et al*[38] randomly assigned 72 patients with high-risk esophageal varices listed for liver transplantation to combined treatment of EBL plus propranolol or propranolol monotherapy. During a mean follow-up of 8 mo, bleeding occurred in 6% patients in the combination group and 31% in the monotherapy group (*P* = 0.03), with 96% and 69% actuarial probability of bleeding-free survival after follow-up, respectively (*P* = 0.04). The authors suggested that combined treatment was superior to propranolol monotherapy regarding both bleeding and bleeding-related mortality. On the contrary, Lo *et al*[39] found no differences in upper gastrointestinal bleeding [26% (*n* = 18) *vs* 18% (*n* = 13), *P* = not significant], variceal bleeding [14% (*n* = 10) *vs* 13% (*n* = 9), *P* = not significant], and mortality [22.9% (*n* = 16) in both treatment groups] between patients treated with EBL combined with nadolol (*n* = 70) and nadolol alone (*n* = 70). Patients in the combination group showed a higher rate of adverse events than in nadolol monotherapy (68% *vs* 40%, *P* = 0.06). Two episodes of variceal bleeding were induced by EBL.

One RCT[40] of 144 patients (11.8% non-cirrhotic portal hypertension), has compared EBL combined with propranolol with EBL monotherapy. In this trial, the probability of bleeding, overall mortality and bleeding-related mortality were comparable between groups. Therefore, according to current evidence, combination treatment of EBL and NSBBs is not recommended for primary prevention.

Isosorbide mononitrate

Isosorbide mononitrate (IsMn) decreases portal pressure by lowering the intra-hepatic resistance through vasodilation and has been evaluated in cirrhosis considering the large number of patients with contraindications or intolerance to b-blockers[41]. The evidence concerning the use of IsMn for primary prevention of variceal bleeding is debatable[42,43]. In a recent meta-analysis[44] the effect of IsMn in primary prevention of variceal bleeding was assessed, comparing IsMn alone *vs* placebo or beta-blockers or EBL and IsMn plus beta-blockers *vs* beta-blockers or EBL. No differences in mortality were observed between IsMn and beta-blockers *vs* β-blockers (49/277 *vs* 50/275; RR = 0.95; 95%CI: 0.68-1.32), or EBL (6/31 *vs* 8/30; RR = 0.73; 95%CI: 0.29-1.84). IsMn increased the risk of bleeding compared to placebo (RR = 2.34; 95%CI: 1.10-4.97) or EBL (RR = 4.33; 95%CI: 1.57-11.92). There were no apparent differences between bleeding rates of patients randomized to IsMn alone or with beta-blockers *vs* beta-blockers or EBL. Meta-analyses of variceal bleeding found a negative effect of IsMn compared to EBL (RR = 3.31; 95%CI: 1.01-10.84), but no apparent dif-

Table 1 Summary on primary prevention of esophageal variceal bleeding			
		Management	Goal of treatment
Cirrhosis		Diagnostic endoscopy for the presence of varices	
No varices		Endoscopic surveillance	Surveillance for development of varices (every 2-3 yr in compensated cirrhosis/yearly in cases of decompensation)
Small varices	Low risk of bleeding	Endoscopic surveillance Or NSBBs	Surveillance for progression of varices (every 1-2 yr in compensated cirrhosis/yearly in cases of decompensation)
	Increased risk of bleeding[1]	NSBBs	Decrease in HVPG of at least 20% from baseline or ≤ to 12 mmHg or resting heart rate of about 55 to 60 beats/min
Medium-large varices		NSBBs Or EBL[2]	NSBBs: Decrease in HVPG of at least 20% from baseline or ≤ to 12 mmHg or resting heart rate of about 55 to 60 beats/min EBL: Variceal obliteration

[1]Child-Pugh B/C cirrhosis or red signs at initial endoscopy; [2]The choice of treatment should be based on local resources and expertise, patient preference and characteristics, side effects, and contra-indications. NSBBs: Non-selective beta blockers; EBL: Endoscopic band ligation; HVPG: Hepatic venous pressure gradient.

ference in variceal bleeding for the remaining treatment comparisons was observed. No effects on bleeding-related mortality were seen for any of the treatment comparisons assessed. Combination of IsMn and beta-blockers increased the risk of adverse events, compared to beta-blockers monotherapy (RR = 1.65, 95%CI: 1.25-2.17), as well as the number of treatment withdrawal (RR = 2.60, 95%CI: 1.55-4.38). Consequently, current evidence does not support the use of nitrates in primary prevention of variceal bleeding.

CONCLUSION

Baveno V[3] recommends both EBL and NSBBs for the prevention of first variceal bleeding (Table 1); however, there is a controversy on which one should be the first choice. Both therapies are equally effective and have no survival difference. Thus, other issues should be considered in order to determine the best therapeutic approach. Prophylactic treatment should have few adverse events, be easy to administer and inexpensive. EBL can cause fatal iatrogenic bleeding, is accompanied by increased expense, needs specialized staff and cannot prevent bleeding from portal hypertensive gastropathy. NSBBs could probably be the first choice in primary prevention, whereas EBL could be reserved for patients with contra-indications, not response, intolerance to NSBBs or lack of compliance to life-time use of drugs. The potent benefit of EBL on patients with refractory ascites should be further investigated.

Lastly, there are issues on the primary prevention of variceal bleeding that require further study including the use of carvedilol, the advancement in ligation devices with better endoscopic field of view and the evaluation of novel therapeutic agents.

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