Primary Prevention of Variceal Bleeding: Pharmacological Therapy Versus Endoscopic Banding

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Abstract

Variceal bleeding is one of the most feared complications in patients with liver cirrhosis. It continues to be a leading cause of death among patients with liver cirrhosis. Although its prognosis has improved over the last several decades, it still carries substantial mortality. Preventing variceal bleeding has been extensively studied and evaluated in several studies in the recent years and the comparison between the different modalities available to prevent variceal bleeding has been an area of discussion. Currently the two most widely used modalities to prevent variceal bleeding are pharmacologic (non-selective beta-blockers [NSBB]) and endoscopic (variceal band ligation [VBL]) which have replaced sclerotherapy in the recent years. In addition to NSBB and recent carvedilol, different other medications have been evaluated including isosorbide mononitrates, spironolactone and angiotensin blocking agents. Comparing the outcomes and adverse effects of these two modalities has been evaluated in different studies. Some studies have showed superiority of VBL until recently, when carvedilol has been included, however; overall mortality has been similar in most trials. Despite that, NSBB remain the first line treatment, as they are cheaper and relatively effective in preventing both esophageal and gastric bleeding. The following sections discuss the primary prevention of variceal bleeding with a focus on NSBB, carvedilol and VBL.

Keywords: Band ligation, Beta-blockers, Esophageal varices, Primary prevention

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Introduction

Liver cirrhosis causes 90% of portal hypertension in the western world, which leads to the development of porto-systemic collaterals, this in turn triggers the formation of the lower esophageal and gastric cardiac varices.[1] Varices are present in 30% of patients with compensated cirrhosis and 60% of those with decompensated cirrhosis.[1] The rate of forming esophageal varices in cirrhotic patients is approximately 7%/year and is higher in decompensated patients.[2,3] The 1-year risk of small variceal bleed is about 5% and can reach up to 15% in large size varices.[4] Despite advances in therapy the overall mortality of variceal bleeding

remains high, it ranges between 20% and 50% depending on the stage and severity of liver cirrhosis.[1,5]

The risk of variceal bleeding depends on several factors such as the size of the varices,[1,2,6] Child-Pugh class and the presence of "red wale sign" (longitudinal dilated venules resembling whip marks). One system is used to predict the risk of a first variceal bleed is the North Italian Endoscopic Club (NIEC), which combines those variables.[7] However, data showed that only a one third of patients who is present with variceal hemorrhage have these risk factors. A prospective study[8,9] indicated that variceal pressure is a strong predictor of the risk of first bleeding episode. Consequently, Combining the NIEC index with variceal pressure may be more accurate to predict the risk of a first episode of bleeding.[8-10]

Other possible independent risk factors include the presence of gastric varices, the patency of the portal and hepatic veins and the velocity and direction of portal flow (as determined with a Doppler ultrasonography).[11] Alcohol abuse has a major role in the occurrence of the first bleeding episode.[12]

Bacterial infection in patients with esophageal varices has been found to increase the risk of bleeding. During an acute bacterial infection there is a release of endotoxin into the systemic circulation, which results in an increase in portal pressure through the production of endothelin and possibly vasoconstrictive cyclooxygenase products. Furthermore endotoxin-induced nitric oxide and prostacyclin release can reduce platelet aggregation and result in further deterioration in the hemostasis.[13]

Management of esophageal varices can be divided into: (1) Primary prevention of variceal bleeding, (2) control of acute bleeding, (3) secondary prevention of bleeding (prevention of recurrent bleeding). In this review, we will summarize the approach to esophageal varices in terms of prevention of the first episode of bleeding.

Prevention of Variceal Bleeding

Every episode of variceal bleed increases the patient's morbidity and mortality. It may also increase the risk of other complications of cirrhosis, such as spontaneous bacterial peritonitis (SBP), hepatorenal syndrome and hepatic encephalopathy. Therefore, primary prophylaxis has emerged as an important practice to prevent variceal bleeding. Current guidelines from the Baveno V Consensus Workshop as well as American Association for the Study of Liver Diseases [Table 1], recommend that all patients with liver cirrhosis should undergo diagnostic upper endoscopy and those who are found to have a high risk esophageal varices should be treated with non-selective beta-blockers (NSBB) or variceal band ligation (VBL) to prevent bleeding [Figure 1].[8,14,15] High-risk patients include those with large esophageal varices (a diameter >5 mm) and patients with small varices who have a Child-Pugh class B or C and/or the presence of "red wale sign".[7,14,15]

Recent studies have identified certain non-endoscopic parameters in an attempt to predict the presence and development of large varices. These parameters include thrombocytopenia, splenomegaly, portal vein diameter, albumin concentration and spider nevi.[16,17] These parameters still lack ideal accuracy and consequently endoscopic screening remains the best method to stratify the risk of bleeding of esophageal varices.[15,18]

Pharmacological Therapy

NSBBs (Propranolol and Nadolol) remain the treatment of choice for prophylaxis for high risk variceal bleeding; overall NSBBs can reduce the risk of the first episode of bleeding from 27% to 17% within 2 years in high-risk cirrhotic patients.[19] NSBBs not only decrease cardiac output, but also induce splanchnic arterial vasoconstriction and therefore reduce splanchnic blood flow.[4,20] NSBBs produce their effect by blocking both beta-receptors (B1 and B2), B1 receptors are located in the cardiac muscles, by blocking those receptors, cardiac contractility and output are reduced. B2 receptors are located in the splanchnic circulation; blocking B2 receptors result in vasoconstriction and reduction of blood flow. Those two actions result in a decrease in the portal pressure and therefore, decrease the risk of bleeding. Other advantages of using NSBBs such as protection against bleeding from hypertensive gastropathy; an uncommon source of gastrointestinal hemorrhagic episodes in cirrhotic patients, they can also prevent ascites and SBP by reducing the portal pressure and bacterial translocation.[21,22]

Table 1: AASLD guidelines on primary prevention of esophageal variceal bleeding[14]
When a patient is diagnosed with liver cirrhosis, screening upper endoscopy is recommended
On upper endoscopy varices can be graded into small or large (>5 mm). The presence of red wale marks should be noted
Patients who do not have varices, BB are not recommended to prevent their development
Patients who have compensated cirrhosis and no varices, upper endoscopy should be repeated in 3 years. If decompensated cirrhosis is found, upper endoscopy should be done at that time and repeated annually
Patients with small varices that have not bled, with Child-Pugh class B/C or have red wale marks, BB should be used to prevent first variceal hemorrhage
Patients with small varices, without Child-Pugh class B/C, or red wale marks, BB can be used although long-term benefit has not been established
Patients with small varices on BB, follow-up endoscopy is not necessary. However, if they are not on BB, upper endoscopy should be repeated in 2 years. If there is evidence of hepatic decompensation, upper endoscopy should be done at that time and annually
Patients with large varices (includes medium/large in previous definition) that have not bled, but have Child-Pugh class B/C or red wale marks, BB or VBL may be recommended to prevent first variceal hemorrhage
Patients with large varices that have not bled with Child-Pugh class A and no red wale mark, BB are preferred, VBL are considered in patients who are intolerant, noncompliant or have contraindications to BB
When patients are on BB, it should be adjusted to maximal tolerated dose, upper endoscopy follow-up is not recommended. If VBL is used then it should be repeated every 1-2 week until obliteration. First upper endoscopy should be performed 1-3 months after obliteration and then every 6-12 months to check for recurrence
Nitrates (either alone or in combination with BB), shunt therapy, or sclerotherapy should not be used in primary prophylaxis of variceal bleeding
AASLD: Association for the study of liver diseases; VBL: Variceal band ligation; BB: Beta-blockers

When NSBBs are used for primary prevention, the dose should be titrated to a resting heart rate of 55-60 beats/min, or side-effects will develop. Another method to evaluate the response to NSBB therapy is to measure the hepatic venous pressure gradient (HVPG). This represents the difference in pressure between the portal and hepatic veins. The target reduction in HVPG is less than or equal to 12 mm Hg or reduction of 20% compared to baseline, pre-treatment levels.[23] Once this target is reached the risk of variceal bleeding is reduced to less than 10%. To assess the validity of HVPG response and variceal bleeding, Villanueva et al.[24] investigated the long-term prognostic value of an acute response to NSBBs and whether the target reduction in HVPG can be improved in primary prophylaxis. In this study, 75 patients (out of 105 patients, 71%) were classified as responders to propranolol (HVPG decreased below 12 mm Hg or less 10% from baseline). Responders had a lower probability of bleeding compared to non-responders after 24 months follow-up (4% vs. 46% $P < 0.001$).

The benefits of NSBBs in large size varices have been established in several studies; however, their use in small size varices is still unclear. Two studies have evaluated if NSBB have an impact on the progression of portal hypertension in patients with small varices. One study randomized 161 patients with small esophageal varices who never bled to receive Nadolol ($n = 83$) or placebo ($n = 78$). The patients were followed for 12-60 months with a mean duration of 36 months. Nine patients were receiving nadolol and had progressed to large varices compared to 29 patients in the placebo group. Overall survival was not different.[25] Another multi-center study randomized 213 cirrhotic patients with portal hypertension without esophageal varices to receive timolol, a NSBB ($n = 108$) or placebo ($n = 105$). In this study timolol had no effect on the development of varices and more adverse events were noted with timolol treated group.[26] The findings of these two studies support the use of NSBBs in the prevention of esophageal bleeding in patients with small size esophageal varices. However, in patients with no varices, NSBB therapy is not indicated and may increase patient's morbidity due to their side-effects.

Recently, carvedilol, a NSBB with a weak intrinsic alpha-1 adrenergic blocking activity, has been shown to reduce the portal pressure through an addition vasodilatory effect through blocking α1 adrenergic receptors. The α1 adrenergic receptors are located in the splanchnic vascular smooth muscles and other sites such as smooth muscles of the genitourinary tract. Blocking α1 adrenergic receptors would lead to a reduction in the intrahepatic vascular tone. Therefore, the addition of α1 blocking activity to non-selective

β-blockers can lead to further reduction of portal pressure.

A study comparing propranolol with carvedilol showed a better reduction in HVPG in the carvedilol treated group ($n = 26$) compared to the propranolol treated group ($n = 25$). 54% versus 23% ($P < 0.05$) achieved a 20% reduction or less than 12 mm Hg reduction in their HVPG, however, side-effects due to hypotension were more frequent in the carvedilol group.[27]

Following that study, more trials have evaluated carvedilol therapy. Tripathi et al.[28] compared carvedilol (77 patients) with VBL (75 patients) in a randomized controlled multicenter trial. In this study carvedilol-treated group was found to have less episodes of bleeding compared to VBL group (10% vs. 23%), however, no difference in the overall survival was noted.

A study by Reiberger et al.,[29] evaluated the response of HVPG to carvedilol in patients who failed to respond to propranolol. In this study 67 patients were categorized as propranolol non-responders out of 104 patients (64%). Of those patients, 38 (56%) achieved hemodynamic response with carvedilol, while the remaining 29 patients were treated with VBL. This study carvedilol was found to have a greater effect on portal pressure when compared to propranolol (19% vs. 12%). Another significant outcome of this study is the lower bleeding rate, hepatic decompensation and consequently deaths in carvedilol treated patients in comparison to VBL treated patients. To address the higher incidents of side effects of carvedilol in Banares study,[27] Reiberger, recommended a dose of 6.25-12.5 mg/day of carvedilol, since higher dosages have resulted in a further decrease of mean arterial pressure and heart rate without additional effect on HVPG.

Other risk factor for variceal bleeding is a bacterial infection.[13] Studies have shown that prophylactic antibiotics can offer certain protection against variceal bleeding.[30,31] On the other hand, studies have found that high portal pressure can lead to SBP, through bacterial translocation through the edematous gut wall.[32] NSBBs were found to decrease the pressure in portal and splanchnic circulation and thus, protect against SBP. Another proposed mechanism for protection in NSBBs is increasing intestinal transit, which leads to decrease bacterial translocation.[33] A meta-analysis by Senzolo et al.,[34] evaluated the possible role of NSBB in preventing SBP. In this study, Senzolo evaluated five studies and the end result showed a significant decrease in the incidence of SBP in propranolol treated patients. Those findings were also found in patients who didn't exhibit any hemodynamic response to propranolol, suggesting another mechanism of protection.

To further demonstrate the pleiotropic effects of NSBBs, a study by Lo *et al.*[35] followed up on patients who either was assigned to NSBBs and Isosorbide mononitrates (IMNs) or VBL for 8 years. Although the incidence of variceal re-bleeding was less in the VBL group compared to the group receiving pharmacological therapy, the overall mortality rate was higher in the VBL group (49% vs. 30%). This raises the question whether NSBBs acting systematically offer some physiologic benefit when reducing the portal pressure over VBL, which aims to prevent the bleeding locally.[35]

The use of NSBBs is generally well-tolerated and if issues arise, these usually resolve after discontinuation of the drug. The side-effects of NSBB do not tend to require hospitalizations or cause fatalities.[36] An issue in the use of NSBB is potentially the high risk of bleeding secondary to a rebound increase in portal pressure once the drug is discontinued due to non-compliance or side-effects.[36]

Although the use of NSBBs has proved to be effective in reducing portal pressure by lowering splanchnic blood flow, 1/3 of patients are classified as non-responders,[37] and even in patients who responded to NSBBs the reduction in their pressure can only reaches 15%,[38] and therefore, other medications have been studied including isosorbide mononitrate, spironolactone, angiotensin converting enzyme inhibitors (ACE) and angiotensin receptor blockers (ARB).

IMN is a vasodilator that has been evaluated as a monotherapy or in combination with NSBB; the idea behind using IMN is to add the drop in HVPG achieved by NSBB. In a multicenter randomized double-blind study 133 patients were enrolled, 67 received IMN and 66 placebo, there was no difference in the incidence of bleeding between the two groups.[39] In one small study, the combination of IMN and NSBB showed a greater reduction in the incidence of variceal bleeding than patients receiving nadolol alone (7.5% vs. 18%).[40] However, a larger study did not confirm these findings. In this study 174 patients were randomized to receive propranolol and placebo and 175 received both propranolol and IMN. This study did not show better results in the combination therapy over propranolol alone.[41]

Spironolactone and low sodium diet theoretically can enhance the response of HVPG to NSBB and reduce the risk of bleeding. However, in a study that compared the efficacy of nadolol and spironolactone with that of nadolol alone showed no difference in risk of bleeding or mortality rate. However, the group that received both nadolol and spironolactone showed less incidence of ascites and other non-bleeding complications of portal hypertension.[42]

ARBs were shown to be effective in reducing portal hypertension in cirrhotic patients in one study,[43] yet, other studies have shown increasing side effects such as hypotension and worsening of kidney function that impeded their use.[44,45] ACE inhibitors have been studied in comparison to NSBB in patients with portal hypertension secondary to cirrhosis through their effect on the renin-angiotensin aldosterone system,[46] ACE inhibitors had more adverse hemodynamic effects in patients with an advanced liver cirrhosis and further studies are needed to evaluate their potential use with or as replacements to NSBB.

VBL

VBL has widely replaced sclerotherapy for the treatment of acute variceal bleeding; it is more effective and has fewer side-effects and requires fewer sessions to eradicate the bleeding vessels. VBL is also used now days for primary prophylaxis to prevent variceal bleeding.

Numerous studies have proved the superiority of VBL in comparison to placebo, for preventing the first episode of variceal bleeding as well as reducing mortality. A prospective trial randomized 126 patients with high-risk varices, who have never bled, to VBL (n = 62) and control group (n = 64). The study found that VBL decreased the 2-year cumulative risk of first esophageal bleeding compared with untreated controls (19% vs. 60%, P = 0.0001), the mortality rate after 2 years was also lower in the VBL group compared with the control group (28% vs. 58% P = 0.001), most deaths in the VBL group were due to other complications of liver failure.[47]

A meta-analysis examined five trails involving 601 high risks patients (all patients had large varices and 1/3 had Child-Pugh class C cirrhosis). VBL reduced the relative risk of bleeding by 64% and the relative risk of death by 45% compared with placebo.[48]

NSBB and VBL have clearly established their benefit in preventing variceal bleeding in comparison with placebo, however, when VBL and beta-blockers (BB) are compared in head to head trials conflicting outcomes resulted. In 2005 four trials comparing VBL with BB have been published,[36,49-51] in three there was no significant difference between VBL and BB[36,49,51] and one trial suggested that VBL treated patients had significantly lower rate of bleeding and mortality than propranolol treated patients.[50] In those four studies the sample size was small and one study[36] was prematurely terminated because of a small sample size.

A meta-analysis evaluated four trials in 2001, included 283 patients, compared VBL with propranolol, the risk of bleeding was reduced by 48% with band

ligation compared to propranolol treated patients, but bleed-related mortality and all-cause mortality were similar in both group.[48]

A recent meta-analysis published in 2012 by Gluud and Krag,[52] included 19 randomized trials, in which 731 patients were randomized to VBL and 733 to NSBB. The overall mortality and bleeding related mortality were not significantly different between VBL and NSBB. However, in terms of preventing variceal bleeding, there was an advantage of VBL over NSBB trials with follow-up period of less than 20 months. A significant finding of this study was when trials with low selection bias were limited for analysis; superiority of VBL over NSBBs could not be established in terms of bleeding. Another explanation for the difference in bleeding and mortality incidences found in this study, takes us back to the aforementioned discussion that NSBBs may have an additional physiological benefit not related to bleeding. This contributes to a decrease in mortality in patients on NSBBs despite having an incidence of bleeding.

Gastric Varices

Gastric varices are less common than esophageal varices, they present in 5-33% of patients of portal hypertension. They can be classified into isolated gastric varices (IGV) and gastro esophageal varices (GOV). IGV occurs without the presence of esophageal varices and are divided into type 1 and 2. Type one (IGV 1) are located in the fundus and type 2 in the body and antrum. GOV can also be divided into type one (GOV 1) which are extensions of the esophageal varices reaching the lesser curvature. GOV 2 are usually longer and found along the fundus.[53]

The incidence of bleeding of gastric varices is about 25% in 2 years. The risks of bleeding are similar to esophageal varices and include the size, Child-Pugh class and the presence of red spots.[11] Primary prevention of bleeding of gastric varices has not been extensively studied. Some studies favored endoscopic treatment[54,55] while other experts recommend NSBBs.[56]

Adverse Events

Both therapies carry risk of morbidity and mortality in general, side effects due to VBL are less frequent than BB. However, adverse events due to VBL are usually severe and may require hospitalization, surgical intervention or blood transfusion. They occurred in 5% of patients and consisted of esophageal perforation, ulcer related bleeding and death.[57] Adverse events related to NSBB occurred in 14% of patients,[57] they were mild and improved once NSBB were discontinued.

Cost effectiveness and quality-of-life should be considered in all patients undergoing therapy and should be individualized according to patient's preference, characteristics and co-morbidities. VBL is a costly procedure, requires many sessions and follow-up endoscopies; on the other hand, BB can cause side-effects that may affect the quality-of-life (fatigue, decreased sexual drive, hypotension, asthma), which can lead to non-compliance. VBL was not found to be cost-effective when compared to NSBBs. However, when quality-of-life was considered in conjunction with cost-effectiveness, VBL became cost-effective.[58]

Summary

Variceal bleeding is one of the most feared complications of esophageal varices secondary to portal hypertension. Therefore every patient diagnosed with liver cirrhosis should undergo upper endoscopy for the detection of esophageal varices and evaluation for risk of bleeding. Patients who are found to have no varices should be followed closely by upper endoscopies every 2-3 years and those who are found to have small size varices can be considered for treatment with non-selective BB for primary prevention of variceal bleeding. Patients who are found to have large size varices (>5 mm) should also be started on BB as a first line prophylactic therapy as they offer several advantages, including low cost, ease of use and safety. If patients do not show a hemodynamic response (by measuring HVPG), develop intolerable side-effects or have any contraindications,
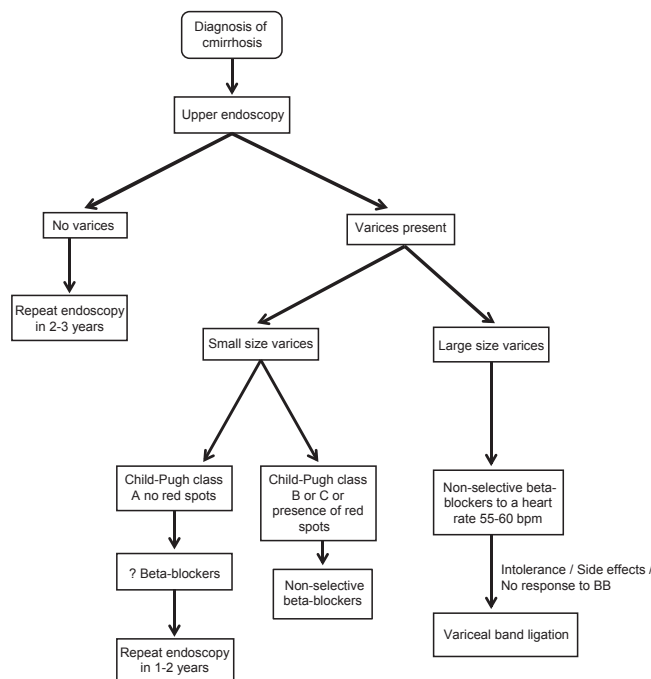
Figure 1: Suggested algorithm for approaching patients with liver cirrhosis for primary prevention of variceal bleeding

then VBL should be considered. Data showed no difference in terms of mortality between those two modalities. Recently carvedilol showed very promising results, with some studies favoring carvedilol over propranolol and VBL and in the future could very well replace propranolol. But further studies to evaluate the long-term effect of carvedilol are needed to confirm its efficacy and become the first line for prevention of variceal bleeding.

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