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REVIEW ARTICLE

Primary prophylaxis of gastroesophageal variceal bleeding: consensus recommendations of the Asian Pacific Association for the Study of the Liver

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Abstract The Asian Pacific Association for the Study of the Liver (APASL) set up a Working Party on Portal Hypertension in 2002, with a mandate to develop consensus guidelines on various clinical aspects of portal hypertension relevant to disease patterns and clinical practice in the Asia-Pacific region. Variceal bleeding is a consequence of portal hypertension, which, in turn, is the major complication of liver cirrhosis. Primary prophylaxis to prevent the first bleed from varices is one of the most important strategies for reducing the mortality in cirrhotic patients. Experts predominantly from the Asia-Pacific region were requested to identify the different aspects of primary prophylaxis and develop the consensus guidelines. The APASL Working Party on Portal Hypertension evaluated the various therapies that have been used for the prevention of first variceal bleeding. A 2-day meeting was held on January 12 and 13, 2007, at New Delhi, India, to discuss and finalize the consensus statements. Only those statements that were unanimously approved by the experts were accepted. These statements were circulated to all the experts and were subsequently presented at the annual conference of the APASL at Kyoto, Japan, in March 2007.

Keywords Varices · Cirrhosis · GI bleed · Guidelines

Abbreviations

APASL	Asian Pacific Association for the Study of the Liver
UGIE	Upper gastro-intestinal endoscopy
HVPG	Hepatic venous pressure gradient
IAP	Intra-abdominal pressure
VBL	Variceal band ligation
ISMN	Isosorbide-5-mononitrate
EIS	Endoscopic injection sclerotherapy
B-RTO	Balloon-occluded retrograde transvenous obliteration
BO-EIS	Balloon-occluded endoscopic injection sclerotherapy

Introduction

The Asian Pacific Association for the Study of the Liver (APASL) set up a Working Party on Portal Hypertension in 2002, with a mandate to develop consensus guidelines on various clinical aspects of portal hypertension relevant to disease patterns and clinical practice in the Asia-Pacific region. In developing these guidelines, the working party was fully aware of and acknowledged the significant contributions made by the four Baveno consensus conferences on portal hypertension [1] and the recent guidelines published by the American Association for the Study of the Liver [2].

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Variceal bleeding is a consequence of portal hypertension, which, in turn, is the major complication of liver cirrhosis [3]. Primary prophylaxis to prevent the first bleed from varices is one of the most important strategies for reducing mortality in cirrhotic patients. Experts predominantly from the Asia-Pacific region were requested to identify the different aspects of primary prophylaxis of variceal bleeding and develop the consensus guidelines. The APASL Working Party on Portal Hypertension evaluated the various therapies that have been used in trials for the prevention of first variceal bleeding. The process for the development of these consensus guidelines contained the following steps: review of all available published literature, a survey of the current approaches for the diagnosis and management in Asia, and discussion on contentious issues and deliberations to prepare the consensus statement by a core group of experts. A 2-day meeting was held on January 12 and 13, 2007, at New Delhi, India, to discuss and finalize the consensus statements. Only those statements that were unanimously approved by the experts were accepted. These statements were circulated to all the experts and were subsequently presented at the annual conference of the APASL at Kyoto, Japan, in March 2007. The working party adopted the Oxford system [4] for developing an evidence-based approach. The group assessed the level of existing evidence and accordingly ranked the recommendations (i.e., level of evidence from 1 [highest] to 5 [lowest]; grade of recommendation from A [strongest] to D [weakest]). A brief background note has been added to explain in more detail the genesis of the consensus statements.

Recommendations

Definitions of varices and variceal bleed prophylaxis

Upper gastrointestinal endoscopy (UGIE) should be performed once the diagnosis of cirrhosis is established and is the gold standard for the diagnosis of varices [2, 5–7]. For definitions relative to prophylactic treatment of gastroesophageal varices, primary prophylaxis relates to offering treatment to prevent the first variceal bleed in patients who have never had any previous variceal hemorrhage [5]. Factors associated with the risk of bleeding from varices include size and wall thickness, the presence of endoscopic stigmata such as red signs (an area where the variceal wall is thin, and therefore weakened), the severity of the liver disease, and the portal pressure [8–12]. Several groups have described different classifications of esophageal varices by size, form, color, and stigmata. In most prophylactic studies, "high-risk" varices have been defined as those that are either moderate or large in size with the presence of *red signs* (*red wale marks*, defined as longitudinal dilated venules resembling whip marks on the variceal surface; *cherry-red spots*, defined as red, discrete, flat spots on varices; and *hematocystic spots*, defined as red, discrete, raised spots). It was felt necessary to define variceal size as either small or large, with large varices being those greater than 5 mm [5]. The group appreciated that the proportion of varices that are at high risk of bleeding, such as small varices but presence of red signs, does not fall within this definition. Because data were limited on the effectiveness of prophylaxis in these special categories of patients, it was felt that they should be reviewed separately and prospective studies be carried out to define their natural history and need for therapeutic interventions.

A lack of clarity exists in the literature on the terminology for the use of prophylactic therapies against variceal bleeding in patients with portal hypertension who have no varices and in those who have small varices. Quite often, early primary prophylaxis has been used for both groups of patients [13]. To clarify the matter, another term *preprimary prophylaxis*, which has been used by some investigators, was suggested. It was felt that clarification of terms would help in proper patient selection for trials and treatment recommendations for practice.

Recommendations

(1.1) "High-risk" varices: Large (>5 mm) varices with at least one of the following red signs: cherry-red spots, hematocystic spots, or red wale markings. (1a)
(1.2) "Low-risk" varices: Small (≤5 mm) varices without red signs. (1a)
(1.3) Varices with these features require further studies to define their risk potential: Large (>5 mm) varices without red signs and small (≤5 mm) varices with red signs. (5, D)
(1.4) Definitions of prophylactic therapies:

Variceal stage	Aim of therapy	Nomenclature	Grade	Level
No varices	To prevent *development* of varices	Preprimary prophylaxis	D	5
Small varices (≤5 mm)	To prevent: (a) *Enlargement* of varices from small to large, or (b) Variceal *bleed*	Early primary prophylaxis	D	5
Large varices (>5 mm)	To prevent *bleed*	Primary prophylaxis	A	1a

Screening for varices

UGIE is considered the gold standard for the diagnosis of varices. Currently, the predictive accuracy of noninvasive methods such as fibrotest, spleen size, portal vein diameter, and transient elastography to reliably detect varices in the esophagus is unsatisfactory [5, 14]. Modalities such as platelet count, platelet count to spleen diameter ratio, and fibroscan could have a good predictive value but need confirmation by further studies. Capsule endoscopy has emerged as a new diagnostic tool and is considered safe and well tolerated, although its sensitivity remains to be established [15, 16]. Its role for screening varices needs further studies.

UGIE should be part of the routine clinical practice once the diagnosis of cirrhosis is made [1, 2, 5–7]. Studies have reported that UGIE is reliable and has shown good agreement between observers for the size of varices and the presence of red signs [17, 18]. In accordance to previous studies, a UGIE every 2 years is considered sufficient for patients without varices [7]. Patients with small varices develop large varices at a rate of 5–12% per year [13, 19]. Decompensated cirrhosis (Child-Turcotte-Pugh B and C), alcohol etiology, or the presence of red signs at the time of baseline UGIE is associated with rapid progression from small to large varices and a more strict surveillance with UGIEs at 1-year intervals is recommended [19]. Mortality due to bleeding is high in patients with high-risk varices (>5 mm in size with red signs), particularly in the presence of severe liver disease (up to 20%). Prophylactic variceal band ligation (VBL) to prevent variceal bleeding should be used in patients with high-risk varices at the time of initial screening. In the intervening period between two endoscopies, modalities for progression of portal hypertension such as platelet count, platelet count to spleen diameter ratio, fibroscan, etc. should be evaluated.

During endoscopic screening, there is good interobserver agreement for size of varices and red signs on the mucosa. No study to evaluate intraobserver agreement in the field of endoscopy has been noted.

Recommendations

(2.1) Because rupture of gastroesophageal varices is associated with high morbidity and mortality, all newly diagnosed cirrhotic patients should be screened for varices. (2a, B)

(2.2.1) Nonendoscopic screening: This has currently not shown to be a consistently effective modality of investigation in screening for varices and to preselect patients for high yield at endoscopy. Modalities such as platelet count, platelet count/spleen diameter ratio, and fibroscan could have a good predictive value, but need confirmation by further studies. (2b, B)

(2.2.2) Endoscopic screening: This is currently the best practice for variceal detection in clinically diagnosed cirrhotic patients and should be carried out on all cirrhotic patients at diagnosis. (2a, B)

(2.2.2.1) Capsule esophageal endoscopy needs further evaluation. (5, D)

(2.3.1) Patients in whom there are no varices should have an endoscopic surveillance every 2 years (2b, B)

(2.3.1.1) The frequency of endoscopic surveillance depends on the severity of liver disease: In decompensated patients, screening should be done more frequently. (5, D)

(2.3.2.1) Varices may progress in size from small to large in 5–12% of cirrhotic patients per year. However, the rate of progression is highly dependent on the severity of liver disease. (2b)

(2.3.2.2) Patients with compensated cirrhosis and small varices (≤5 mm) at initial endoscopy should undergo endoscopic surveillance at 1-year intervals. (5, D)

(2.3.3.1) Mortality due to bleeding is high in patients with high-risk varices (>5 mm in size with red signs), particularly in the presence of severe liver disease (up to 20%). (2b)

(2.3.3.2) Prophylactic VBL to prevent variceal bleeding should be used in patients with high-risk varices at the time of initial screening. (1a, A)

(2.4.1) Interobserver variation in endoscopic screening: Good agreement for the size of varices and red signs on the mucosa has been observed between different observers. (2a)

(2.4.2) Intraobserver variation in endoscopic screening: No intraobserver agreement study in the field of endoscopy has been noted. (5)

(2.5) In the intervening period between two endoscopies, modalities for progression of portal hypertension such as platelet count, platelet count to spleen diameter ratio, fibroscan, etc. should be evaluated. (5, D)

Preprimary prophylaxis

Groszmann et al. [13] conducted a large, multicenter, double-blind, randomized placebo-controlled trial. A total of 213 cirrhotic patients were enrolled. The trial failed to show benefits of nonselective β-blockers (timolol) in the prevention of varices in patients with portal hypertension (hepatic venous pressure gradient [HVPG] > 5 mm Hg) who had not yet developed varices. An HVPG of more than 10 mm Hg at baseline and at 1 year after the inclusion in the study was highly predictive of the development of primary, secondary, and terminating events ($P < 0.001$). A significantly larger number of patients with moderate or severe adverse events were observed in the timolol group

(48%) than in the placebo group (32%). Severe adverse events occurred in 20 (18%) patients in the timolol group and in 6 (6%) patients in the placebo group. Hence, it is concluded that universal use of β-blockers in cirrhosis is not recommended to prevent formation of varices. Preprimary prophylaxis is still a research field and, therefore, it is recommended that portal pressure estimation by HVPG measurement should be included in future clinical trials.

Recommendations

(3.1) The formation of varices is predicted by HVPG and severity of liver disease. (2a)
(3.2.1) Present data do not recommend treatment of patients with cirrhosis who do not have varices to prevent the formation of varices. (1b, A)
(3.2.2) These patients should be monitored for the formation of varices. (5, D)
(3.2.3) They can be entered into trials of preprimary prophylaxis. (5, D)

Early primary prophylaxis

Patients with small varices develop large varices at a rate of 12% at 1 year and 31% at 3 years. Decompensated cirrhosis (Child-Turcotte-Pugh B and C), alcohol etiology, or presence of red signs at the time of baseline UGIE is associated with rapid progression from small to large varices [19]. Previous trials reporting on the pharmacologic prophylaxis of small esophageal varices have included a total of 179 patients. Heterogeneity in both the classification of varices and the number of bleeding episodes in this subgroup is small [20–26]. The only two available studies, specifically addressing the issue of the efficacy of nonselective β-blockers in preventing the enlargement of small varices, have contradictory results. In the first study by Cales et al. [25], the 2-year proportion of patients with large varices was unexpectedly larger in the propranolol group than in the placebo group (31% vs. 14%, $P < 0.05$). However, the study enrolled patients with no and small varices, and a large number of the patients failed to have a regular follow-up. Another large multicenter, placebo-controlled, but single-blinded trial by Merkel et al. [26] showed that patients with small varices treated with nadolol had a significantly slower progression to large varices (11% at 3 years) than patients who were randomized to placebo (37% at 3 years), with no differences in survival. These encouraging results are in clear contrast to the previous study. However, in this study too a large percentage of patients on β-blockers had to be withdrawn from the study because of adverse events as compared with placebo (11% vs. 1%, $P < 0.05$). It was concluded that prophylactic treatment with nonselective β-blocker can be considered in patients with small varices who are at a high risk for bleeding, that is, those with advanced liver disease and the presence of red signs on varices. No role of VBL is reported in preventing enlargement or bleeding in patients with small varices.

Recommendations

(4.1) Variceal size progresses at a rate of 5–12% per year, and the rate is higher in patients with severe liver disease. (2b)
(4.2.1) β-Blocker prophylaxis to prevent variceal enlargement or bleeding may be started in compensated cirrhosis with small varices. (1b, A)
(4.2.2) Cirrhotic patients, with small varices having red signs or small varices with decompensated liver disease, should be offered β-blocker therapy. (5, D)
(4.3) No role of VBL is reported in preventing enlargement or bleeding in patients with small varices. (5, D)

Prevention of first variceal bleed: general measures

The primary prophylaxis of variceal bleed has been mainly the VBL and nonselective β-blockers. Apart from the pharmacologic agents, certain activities or maneuvers have been found to influence portal and variceal pressure. Mechanical increase of intra-abdominal pressure (IAP) markedly increases the azygous blood flow (an index of gastroesophageal collateral blood flow) and variceal pressure and tension. These observations are compatible with the concept that reducing a high IAP may have a beneficial effect on prevention of variceal bleeding and transient increase in IAP may lead to variceal bleeding [27–32]. These findings suggest that it may be wise to advise patients with cirrhosis and portal hypertension to avoid activities that cause marked increases in IAP such as lifting heavy objects and straining while defecation. Total volume paracentesis may decrease variceal pressure and may improve portal hemodynamics, which restores within 24 h of total volume paracentesis [28, 29]. However, more trials are needed before it can be recommended to routinely perform total volume paracentesis in patients with esophageal varices to decrease bleeding risk.

It was suggested that cirrhotic patients with portal hypertension should be informed of potential risks of bleeding during strenuous exercise. Propranolol therapy may protect from the deleterious effects of a moderate physical exercise on portal hemodynamics at the expense of reduction of liver perfusion in patients with cirrhosis [33, 34].

Acute ethanol consumption may cause variceal bleeding. Reports on the effects of alcohol on the portal hemodynamics were conflicting. This discrepancy was

possibly related to different study design and different dose used in studies [35, 36]. Nonetheless, it is wise to abstain from alcohol to prevent progression of liver disease.

Postprandial hyperemia may increase risk of variceal bleeding. It might be blunted by octreotide and isosorbide-5-mononitrate (ISMN), whereas propranolol decreases only baseline HVPG [37–40].

Pharmacologic drugs might influence the risk of variceal bleeding [41–44]. Two previous interview-based studies [41, 42] had demonstrated that aspirin, used alone or in combination with other nonsteroidal anti-inflammatory drugs, was significantly associated with first variceal bleeding episode in patients with cirrhosis. Therefore, it was suggested, given the life-threatening nature of variceal bleed, that the possible benefit of aspirin treatment should be weighed against the risk of this complication. Prospective controlled trials are required to eliminate the potential interview and recall bias of previous studies [41–44].

In summary, whether the beneficial hemodynamic effects of avoidance of increase in IAP, total paracentesis, and avoidance of moderate exercise can be translated into effective primary prophylaxis of esophageal bleed is not known. Controlled trials are required to justify these strategies for primary prophylaxis of esophageal variceal bleed.

Recommendations

(5.1) Risk of variceal bleeding increases with increase of variceal pressure. (1b)
(5.2) Changes of HVPG predicts the risk of variceal bleeding. (1b)
(5.3.1) Lifting heavy objects, straining at defecation, stretching, and coughing, and the Valsalva maneuver may cause marked increase in variceal pressure. (2c)
(5.3.2) Patients with esophageal varices should avoid activities that cause increase in variceal pressure, such as lifting heavy objects, straining at defecation, stretching, and coughing, to avoid variceal bleeding. (2c, B)
(5.4.1) Total volume paracentesis may decrease variceal pressure and improve portal hemodynamics, which restores within 24 h of total volume paracentesis. (2c)
(5.4.2) Further trials are needed before routine total volume paracentesis can be recommended to prevent variceal bleeding in patients with esophageal varices. (5, D)
(5.5.1) Moderate exercise may increase HVPG and decrease hepatic blood flow. (2c)
(5.5.2) Propranolol therapy may protect from the deleterious effects of a moderate physical exercise on portal hemodynamics at the expense of reduction of liver perfusion in patients with cirrhosis. (2c, B)
(5.5.3) Cirrhotic patients with portal hypertension should be advised of potential risk of bleeding during moderate exercise. (5, D)
(5.6.1) Postprandial hyperemia increases HVPG. (2c)
(5.6.2) Postprandial hyperemia may increase the risk of variceal bleeding. (5)
(5.6.3) Postprandial hyperemia might be blunted by octreotide and ISMN. Propranolol decreases only the baseline HVPG. (2c, B)
(5.7.1) Effect of acute ethanol consumption on portal hemodynamics is not conclusive. (2c)
(5.7.2) Acute ethanol consumption may cause variceal bleeding. (5)
(5.7.3) Although, there is no conclusive effect of ethanol on portal hemodynamics, it is wise to abstain from alcohol. (5, D)

Primary prophylaxis for large esophageal varices

Primary prophylaxis reduces the risk of variceal bleeding in patients with medium to large varices. Nonselective β-blockers such as propanolol and nadolol lower portal pressure by reducing cardiac output (β_1 blockade) and allowing unopposed α-adrenergic activity to promote splanchnic vasoconstriction (β_2 blockade). Primary prophylaxis with nonselective β-blockers reduces both the rate of variceal bleeding and bleeding-related mortality. Meta-analysis of studies comparing β-blocker therapy with placebo has shown that nonselective β-blockers reduce the incidence of initial bleeding by approximately 50% (bleeding rate 30% in controls vs 14% in β-blocker-treated patients) and one bleeding episode is prevented for each 10 patients treated [45, 46].

In some centers, HVPG measurements have been used to distinguish "responders" from "nonresponders" to β-blocker therapy. Assessment of hemodynamic response (decrease in HVPG to 12 mm Hg or less or decrease by at least 20% of baseline values) to drugs is the best predictor of efficacy of prophylaxis of variceal bleeding in patients treated with β-blockers or other portal pressure-reducing drugs [47–52].

Endoscopic injection sclerotherapy (EIS) has been shown to be effective in preventing variceal bleeding in some studies, but now it has been largely replaced by VBL because of fewer adverse effects. Studies of VBL for primary prophylaxis that include patients with high-risk esophageal varices have shown that VBL significantly reduces the risk of first variceal bleeding and that serious adverse effects are uncommon [53–57]. A meta-analysis of five studies of VBL versus placebo suggested that VBL reduces the risk of first variceal bleed, bleeding-related mortality, and overall mortality [58]. Some studies have

shown a very low rate of bleeding with VBL compared with β-blockers [18, 57]. It has been argued that this may reflect a high level of experience and technical expertise among the investigators in these studies that is not achievable in routine practice. Recent cost-effectiveness studies have shown that β-blockers were a cost-effective form of prophylactic therapy, while this was not shown for VBL [59].

A number of simple measures exist that may improve the results of VBL and increase its safety and efficacy compared with those of β-blockers. These include using proton pump inhibitors or sucralfate to reduce esophageal ulceration [60], using multibanders, and increasing the interval between banding sessions [61].

Whether VBL should be used as first-line therapy in preference to β-blocker remains controversial [62]. Various published randomized trials comparing the efficacy and safety of VBL and β-blockers in primary prophylaxis exist [53–57, 63–67]. A recent meta-analysis suggests that VBL has greater efficacy in preventing initial bleeding with a 34% relative risk reduction than do β-blockers. However, mortality is same in both treatment groups [68]. The possible benefits of VBL in reducing initial bleeding rates need to be weighed against the low cost and ease of use of β-blockers [62]. Approximately 25% of patients suffer transient adverse effects following VBL such as dysphagia and chest discomfort, and there is a small risk of life-threatening bleeding from esophageal ulcerations [55, 58, 68].

The combination of a nonselective β-blocker and VBL for primary prophylaxis was compared with VBL alone in a randomized trial performed in patients who had high-risk varices. No differences were reported in the incidence of bleeding or death between the groups. The varices recurred more frequently in the VBL-alone group, whereas adverse effects were more common in the combination group [69].

Although, in one study, ISMN was shown to be as effective as propranolol in the primary prophylaxis, long-term follow-up in the ISMN group revealed that mortality was increased by this therapy in patients who were older than 50 years [22, 70, 71]. Subsequent trials in patients who were intolerant to β-blockers showed that ISMN increased the risk of bleeding at 1 and 2 years compared with patients receiving no treatment, although this did not affect survival. Furthermore, adverse effects were more frequent in patients receiving ISMN [23, 72]. Therefore, it was concluded that nitrates alone should not be used in patients with cirrhosis for primary prophylaxis. In one unblinded study, a significantly lower rate of first hemorrhage was noted in patients receiving combination therapy with nadolol plus ISMN than with nadolol alone [24, 73]. However, this finding was not confirmed in larger double-blinded, placebo-controlled trials that also showed that adverse effects are more common with combination therapy than with β-blockers alone [74, 75]. Therefore, it was concluded that a combination of a β-blocker and ISMN could not be recommended for primary prophylaxis.

Recommendations

(6.1) Primary prophylaxis reduces the risk of variceal bleeding in patients with medium to large varices. (1a)
(6.2) VBL and nonselective β-blockers are effective primary prophylactic therapies. (1b)
(6.3) β-Blockers reduces the risk of primary variceal hemorrhage and bleeding-related mortality compared with no treatment. (1a)
(6.4) VBL reduces the risk of primary variceal bleeding, bleeding-related mortality, and overall mortality compared with no treatment. (1a)
(6.5) VBL reduces the risk of initial bleeding episodes compared with β-blockers, but there is no survival advantage. (1a)
(6.6) The addition of β-blockers to VBL does not further reduce the risk of primary bleeding, but it does reduce variceal recurrence rates. (1b)
(6.7) ISMN monotherapy has no role in primary prophylaxis. (1a)
(6.8) ISMN can lower portal pressure when added to β-blockers, but evidence that a combination of the two drugs reduces the risk of bleeding compared with β-blockers alone is lacking. (1b)
(6.9) Patients with large varices should be treated with nonselective β-blockers, preferably with monitoring of HVPG or VBL to prevent initial variceal bleeding. (1a, A)
(6.10) Patients with large varices who are intolerant to or nonresponsive to β-blockers should be offered VBL. (5, D)

Primary prophylaxis for gastric varices

Gastric varices can occur alone or in combination with esophageal varices [76]. The incidence of first-time bleeding from gastric varices (especially GOV2 and IGV1) in patients who have never received treatment is about 10–25% [76, 77]. Patients with gastric variceal hemorrhage bleed more profusely and have higher mortality than those who bleed from esophageal varices [76–79]. Independent factors that predict high risk of bleeding from gastric varices are diameter of 5 mm or more, Child-Turcotte-Pugh class B or C, and varices with red signs [79–81]. To date, there is no reported randomized controlled trial of pharmacologic therapy for primary prophylaxis of bleeding from gastric varices. Nonetheless, it may be acceptable practice to use nonselective β-blockers for primary prophylaxis in patients with gastric varices because it would be logical to assume that reduction in HVPG should have beneficial effects [82].

EIS for gastric varices, although resulting in significantly improved hemostasis when using *N*-butyl-2-cyanoacrylate compared with other sclerosants, can result in bleeding from the injection site and rebleeding from the rupture site [76, 83–86]. Pulmonary, cerebral and coronary emboli may occur during cyanoacrylate injection of gastric varices [87, 88]. On current evidence, the use of EIS or VBL alone is not justified for primary prophylaxis against gastric variceal bleeding because there are issues of safety related to the use of both these procedures.

Balloon-occluded retrograde transvenous obliteration (B-RTO) has been shown to be effective and safe in obliterating gastric fundal varices, with a success rate in about 90% of cases and a variceal recurrence rate of less than 7% [89–92]. B-RTO is also effective for duodenal varices with lienorenal shunt. Complications of B-RTO include transient fever, transient worsening in liver biochemistry, hemoglobinuria, abdominal pain, pleural effusion, atrial fibrillation, risk of hepatic and renal toxicity, shock, and embolism due to the relatively large volume of sclerosant that must be injected. A potentially problematic long-term sequel of B-RTO is the observed development or worsening of esophageal varices in up to 50% of patients [93]. It has been shown that treatment with haptoglobin reduces the risk of hemoglobinuria after B-RTO [94, 95]. A recent randomized controlled trial of 20 patients has shown that balloon-occluded endoscopic injection sclerotherapy (BO-EIS) was as effective as B-RTO and required less sclerosant in comparison with B-RTO and was safe for prophylactic treatment of high-risk gastric fundal varices [91]. Concomitant hepatocellular carcinoma is the most important prognostic factor after B-RTO [94, 95]. It was concluded that primary prophylaxis for high-risk gastric varices would reduce the probability of bleeding and the associated mortality. However, more randomized controlled trials should be conducted in patients with gastric varices.

Recommendations

(7.1.1) Gastric varices (GOV2 and IGV1) at high risk of bleeding are:

- varices 5 mm or more in diameter. (5)
- varices with red spots. (1b)
- varices in Child-Turcotte-Pugh class B or C liver cirrhosis. (1b)

(7.1.2) Because probability of bleeding and associated mortality are high, primary prophylaxis for high-risk gastric varices is justified provided procedure is safe and effective. (5, D)

(7.2) In the absence of randomized controlled trials, it is acceptable to use nonselective β-blockers for primary prophylaxis for gastric varices because a reduction of HVPG would have beneficial effects. (5, D)

(7.3) Endoscopic procedures, EIS and VBL, used alone are not suitable for primary prophylaxis in gastric variceal bleeding. (5, D)

(7.3.1) Data are insufficient regarding the use of cyanoacrylate for primary prophylaxis of gastric variceal bleed. (4, C)

(7.4.1) Balloon-occluded procedures, BO-EIS and B-RTO, are effective and safe. (1b)

(7.4.2) B-RTO may be considered for high-risk gastric varices in centers where expertise exists. (2b, B)

(7.4.3) B-RTO is effective for duodenal varices with lienorenal shunt. (4, C)

(7.4.4) Size of esophageal varices may increase after B-RTO. (3b, B)

(7.4.5) Treatment with haptoglobin reduces the risk of hemoglobinuria after B-RTO. (3b, B)

(7.4.6) Concomitant hepatocellular carcinoma is the most important prognostic factor after B-RTO. (3b, B)

Role of HVPG in primary prophylaxis

In patients on drugs for prevention of variceal bleeding, it has been shown that a decrease in portal pressure, expressed as a decrease in HVPG, is a good predictor of clinical efficacy. Decrease in HVPG to 12 mm Hg or less or decrease by at least 20% of baseline values is associated with low risk of variceal bleeding [47–50]. Poor hemodynamic response was found to be the main factor predicting bleeding. HVPG response to drugs is the best predictor of efficacy of prophylaxis of variceal bleeding in patients treated with β-blockers or β-blockers plus nitrates [22, 47, 51, 70, 73, 74]. The clinical value of HVPG remains unchanged, even when other confounding factors such as the size of varices, presence of red signs, or North Italian Endoscopic Club index were taken into consideration. It was found that in the prediction of effectiveness of treatment, the hemodynamic response is much more useful than the initial size of varices and the presence of red signs [47].

HVPG measurement, although invasive, is safe and relatively simple. The information obtained may be predictive of occurrence of first variceal bleeding and potentially can help in determining whether pharmacologic therapy is effective [50]. We need a safe and accurate noninvasive method for the measurement of portal pressure. Until this goal is achieved, HVPG measurement remains the only way to assess responses to pharmacologic therapy and to develop a tailored approach to prevent variceal bleeding in patients with portal hypertension. HVPG is recommended for identifying patients with high risk of variceal bleeding and nonresponders to

pharmacotherapy. However, HVPG has limitations of being invasive and not being widely available, and hence its routine use in clinical practice cannot be recommended.

Recommendations

(8.1) HVPG is a good predictor of the risk of first variceal bleed. (1a)
(8.2) Reduction of HVPG to 12 mm Hg or less or 20% reduction from baseline reduces the risk of first bleed. (1a)
(8.3) HVPG can reliably distinguish responders from nonresponders to pharmacotherapy. (1a)
(8.4) HVPG is recommended in identifying patients with high risk of variceal bleeding and nonresponders to pharmacotherapy. (1a, A)
(8.4.1) However, HVPG has limitations of being invasive and not being widely available, and hence its routine use in clinical practice cannot be recommended. (5, D)

Recommendations for pediatric patients

The spectrum of portal hypertension is different both in adults and in children. The spectrum also varies from country to country. In the West, intrahepatic causes of portal hypertension are common in children, whereas in the East, portal hypertension in children is mainly due to extrahepatic portal venous obstruction [96–103]. Endoscopic screening is still the best option in children for detecting varices. All children with cirrhosis should have a screening endoscopy for varices at diagnosis. No well-established approaches exist for preprimary and early primary prophylaxis in children. At present, only a few studies have been reported on primary prophylaxis of variceal bleeding in children [101–106]. In one retrospective study, propanolol was used in children with portal hypertension for prevention of variceal bleeding [106]. Data are insufficient to recommend the use of nonselective β-blockers as standard clinical practice in children. The pressing need for conducting a large controlled trial of β-blockers in children with portal hypertension cannot be overemphasized. Only one study on VBL for primary prophylaxis in children is reported [105]. We do not have any information whether combination of β-blockers and VBL is superior to either one of them alone.

Recommendations

(9.1) All children with cirrhosis should have a screening endoscopy for varices at diagnosis. (5, D)
(9.2) No well-established approaches exist to preprimary and early primary prophylaxis in children. (5)
(9.3) β-Blockers without prior assessment of the presence of esophageal varices are not recommended. (5, D)
(9.4) VBL is safe in preventing first variceal bleeding in children with large varices. (4, C)
(9.5) Data are insufficient to recommend the use of nonselective β-blockers as standard clinical practice in children. (4, C)
(9.6) An urgent need exists for large prospective randomized controlled trials in children to assess efficacy of VBL and β-blockers for primary prophylaxis of variceal bleeding. (5, D)

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