REVIEW ARTICLE

Prevention of Variceal Bleeding:Current Concepts

S PERVEEN[a], SMB HOSSAIN[b], MA AHMED[c], AM SIDDIQUE[d], MG RABBANI[e], M NAZIMUDDIN[f]

(J Bangladesh Coll Phys Surg 2004; 22 : 21-30)

Introduction :

Bleeding from varices is a very serious complication in cirrhotic patients,with a mean mortality rate around 30%[1]. If the portal vein pressure is decreased by pharmacological therapy the varices will not bleed and progressively decrease in size. The portal hypertension in cirrhotic patients develops as a consequence of two mechanisms: the increase of portal inflow and the increase of intrahepatic resistance. Variceal haemorrhage accounts for one third of all deaths related to cirrhosis. Patients surviving a variceal bleed are at high risk of rebleeding over 60% at one year and mortality from each rebleeding is about 20%[1-3].

Portal hypertension can be attenuated by decreasing intrahepatic resistance,reducing portal blood flow or both. Non-selective beta -blockers (propranolol and nadolol) effectively prevent variceal bleeding by reducing portal pressure and blood flow within the portal system[4,5]. Since increased vascular tone, partly due to reduced release of nitric oxide in the hepatic circulation,contributes significantly to increase hepatic resistance to portal flow in cirrhosis, it is rational to use vasodilators in the treatment of portal hypertension.Isosorbide-5-mononitrate (ISMN) is the only drug that has been tested in the randomized trials [6,7]. Losartan, an angiotensin II receptor blocker, has portal hypotensive effect. Losartan is as effective as propranolol in reducing portal pressure in cirrhotic patients who are not receiving diuretics[8].

a. Major Shaila Perveen, FCPS, Classified Specialist in Medicine, CMH, Dhaka
b. Col. Sk. Md. Bahar Hossain, FCPS, DCP, Classified Specialist in Medicine, CMH, Dhaka
c. Major Mir Azimuddin Ahmed, MCPS, DCP, Graded Specialist in Pathology, Armed Forces Institute of Pathology, Dhaka.
d. Major Gen. Abdul Moyeed Siddique, FCPS, FRCP, Consultant Physician, Bangladesh Armed Forces
e. Brig. Gen. MG Rabbani, FCPS, Chief Physician, CMH, Dhaka
f. Col. Md. Nazimuddin, Personal Physician to the Honourable Prime Minister, Prime Minister's Office, Tejgaon, Dhaka

Address of correspondence : Dr (Major) Shaila Perveen, Classified Medical Specialist, CMH, Dhaka, Asst. Personal Physician to the Honourable Prime Minister, Prime Minister's Office, Tejgoan, Dhaka.

Local treatments act at the variceal bleeding site,without modifying the underlying pathophysiological abnormalities leading to haemorrhage.The best examples are endoscopic procedures like endoscopic injection sclerotherapy (EIS),endoscopic band ligation (EBL),variceal obturation with bucrylate and surgical techniques such as oesophageal transection or devascularization [9-12]. These procedures are often effective only for a short time, since portal pressure and blood flow remain unchanged, and varices frequently recur (about 50% at two years)[9]. Shunt surgery has been used for almost 50 years and is based on the simple concept of bypassing the site of increased resistance. It is effective at decreasing the risk of variceal rebleeding but has the disadvantage of enhancing encepahalopathy and worsening liver failure. Selective shunts such as the distal splenorenal shunt (DSRS) or calibrated shunts aim to reduce this problem[9,13-15].

Target hepatic venous pressure-gradient (HVPG) to prevent variceal bleeding:

Clinically significant portal hypertension is defined by a portal pressure gradient measured as hepatic venous pressure gradient (HVPG) above 12 mm of Hg[1]. Variceal bleeding rarely, if ever, occurs below this threshold pressure. Haemodynamic studies have shown that if HVPG is decreased below this threshold, the patient has a lower risk of variceal bleeding. Moreover many studies show that if drug therapy achieves a reduction in HVPG of at least 20% of the baseline value, even without reaching values below 12 mm of Hg, the residual risk of variceal bleeding is low, about 10% at 2 years. The risk appears similar to that reported for patients treated with surgical shunts or with transjugular intrahepatic portosystemic shunt (TIPS)[3,11,16,17].

Primary prophylaxis of variceal haemorrhage:

Pharmacologic therapy is the current standard of treatment for primary prophylaxis of esophageal variceal bleeding. Patients with medium or large varices should be treated with a non selective beta

Journal of Bangladesh College of Physicians and Surgeons Vol. 22, No. 1, January 2004

Table -I

Reported rebleeding and mortality in randomised trials:

Treatment	Number of studies	Rebleeding rate	Mortality rate
Untreated	19	55-67%	23-54%
Beta blockers	26	37-57%	13-39%
EIS	54	34-53%	18-36%
EIS + Beta blockers	13	19-49%	7-26%
EBL	18	20-43%	19-34%
Beta blockers + ISMN	6	30-42%	12-32%
TIPS	14	12-22%	18-35%
DSRS	9	11-31%	22-55%

Table-II

Risk of rebleeding in responders versus Non-responders on drug therapy:

Series In non-responders	Drug	Non-responders	Rebleeding rate in responders	Rebleeding rate
Feu et al	Propranolol	64%	54%	8%
Escorsell et al	Propranolol	62%	44. 8%	6%
Villanueva et al	Nadolol + ISMN	55%	47%	7%
Bureau et al	Propranolol + ISMN	41%	64%	10%

Table-III

Endoscopic sclerotherapy compared with no specific treatment for the primary prevention of bleeding from the varices: (n-166, Followup period -32 months)

Treatment	n	At one year		At 3 year	
		Bleeding	Survival	Bleeding	Survival
Endoscopic Sclerotherapy :	84	16%	87%	33%	62%
No specific treatment:	82	16%	84%	29%	62%

blocker with the dose titrated to achieve a 25% decrement in resting heart rate or a heart rate of 55 to 60 bpm[18]. The development of symptoms will, of course, limit the dose used. The therapeutic end points are not well correlated with decreases in portal pressure. Measurement of the HVPG before therapy and after 3 months of therapy provides a rational approach to drug dosing. If the HVPG decreases by 20% or to less than 12 mm of Hg, the medication dose will be effective in preventing haemorrhage. If,

however, the HVPG is not appropriately lowered, a long-acting nitrate may be added. Patients with small varices should be observed, with endoscopic examinations every 2 years to assess progression of variceal size. Endoscopic therapy is not indicated for the primary prevention of variceal bleeding[18,19].

Reducing the portal pressure by at least 20% or to a HVPG of less than 12 mm of Hg is associated with significant protection against bleeding. In the absence of a determination of the HVPG, the dose of beta-blockers is titrated on the basis of clinical assessment. In addition to their side effects, an important problem with beta-blockers is their variable effects on portal pressure and the consequent difficulty in predicting a clinical response. The effectiveness of beta -blockers for primary prophylaxis against variceal bleeding has been demonstrated in several controlled trials. In addition, meta analysis have revealed a 40 to 50% reduction in the risk of bleeding and a trend toward improved survival. An analysis comparing propranolol with sclerotherapy and shunt surgery found propranolol to be the only cost effective form of primary prophylaxis[9,20-22]. In addition to beta-blockers, a number of vasodilators have been investigated in patients with portal hypertension. Isosorbide mononitrate (ISMN) has received the greatest attention. The mechanism of action of ISMN is unclear but they may reduce intrahepatic resistance, reduce portal pressure by means of reflux splanchnic arterial vasoconstriction in response to vasodilatation in other vascular beds or both[23,24].Unfortunately ISMN can not currently be recommended as monotherapy even for those with an intolerance of beta-blockers because of their potential to accentuate vasodilative hemodynamics typical of cirrhosis [25]. But the addition of ISMN to propranolol results in an enhanced reduction in portal pressure and may improve protection against variceal bleeding[24].

Endoscopic therapies have assumed a prominent role in the treatment of esophageal varices.Endoscopic sclerotherapy, most often with ethanol, morrhuate sodium, polidocanol or sodium tetradecyl sulfate has been used extensively. Most of the trials have shown no advantage of sclerotherapy in primary prophylaxis [9,25,26]. A recent trial comparing propranolol with endoscopic variceal ligation for primary prevention of variceal bleeding revealed that the actuarial rate of bleeding was 43% with propranolol and 15% with ligation. Ligation is an acceptable option for patients at high risk of variceal bleeding who have an intolerance of or contraindication to medical therapy [9].

Prevention of variceal rebleeding:

After an episode of acute variceal bleeding, patients are at high risk for recurrent bleeding and death. Thus therapy to prevent recurrent bleeding is essential. Variceal haemorrhage recurs in approximately two thirds of patients, most commonly within the first six weeks after the initial episode[1, 9]. Clinical predictors of early recurrence include the severity of the initial hemorrhage, the degree of liver decompensation and the presence of encephalopathy and impaired renal function. Endoscopic features predictive of early recurrence include active bleeding at the time of the initial endoscopy, stigmata of recent bleeding and large varices. In addition, the severity of portal hypertension, measured by the HVPG, correlates closely with the risk of recurrent bleeding as well as with the actuarial survival rate after an initial variceal hemorrhage[9].

Given the risk of recurrent hemorrhage and its associated morbidity and mortality,secondary prophylaxis should be instituted after the initial episode. Treatment modalities to prevent variceal bleeding include (i) pharmacological treatment with non selective beta blocker (propranolol and nadolol), Isosorbide mono nitrate (ISMN), losartan or combination pharmacotherapy (beta blocker with ISMN). (ii) Endoscopic techniques which include a. Endoscopic injection sclerotherapy (EIS) b. Endoscopic band ligation (EBL).(iii) Transjugular in trahepatic portosystemic shunt (TIPS), (iv). Portacaval shunt operations. (v). Oesophageal transection or devascularization and (vi). Liver transplantation[9].

Pharmacotherapy:

A number of pharmacological agents that reduce portal pressure have been proposed for use in secondary prophylaxis but the only ones for which there is sufficient evidence of efficacy are beta-blockers[27-30]. Several randomized placebo controlled trials, including a meta analysis,have demonstrated

Journal of Bangladesh College of Physicians and Surgeons Vol. 22, No. 1, January 2004

that non-selective beta-blockers decrease the risk of recurrent bleeding and prolong survival. It has been customary to adjust the dose of beta-blockers to achieve a 25% fall in the resting heart rate. But this reduction by no means guarantees an effective fall in HVPG,and there is no correlation between changes in heart rate and changes in HVPG.The most rational approach is to titrate up the dose of beta-blockers to the maximum tolerated dose with dose escalation every two days[1].

Until recently, drug therapy was based on the use of vasoconstrictors that reduce portal pressure and blood flow within the portal system.Non-selective beta-blockers eg. propranolol,nadolol act by this mechanism. It is rational to use vasodilators along with beta-blockers in the treatment of portal hypertension.ISMN is an important drug that has been tested in randomized trials.ISMN releases nitric oxide and reduces intrahepatic resistance[24,31-33]. The addition of ISMN to beta-blockers appears to enhance the protective effect of beta-blockers alone for the prevention of recurrent variceal bleeding but offers no survival advantage and reduces the tolerability of therapy.Some non responders will respond with the addition of a second drug.The addition of ISMN to a beta-blocker enhances the fall in portal pressure achieved by beta-blockers alone.About one-third of non-responders to beta-blockers become responders after addition of ISMN[1,9].

Losartan is as effective as propranolol in reducing portal pressure in cirrhotic patients. Losartan is also superior to propranolol for achieving target level HVPG for prevention of variceal bleeding in non-ascitic cirrhotic patients[8].

ISMN alone in the prevention of variceal rebleeding;
Nonselective beta-blockers are very effective in preventing variceal bleeding in patients with cirrhosis of liver. However 15-25% of patients have contraindications or develop severe side effects precluding its use. One hundred thirty-three consecutive cirrhotic patients with esophageal varices and contraindications or intolerance to beta-blockers were included in a multicenter, prospective, double-blind randomized controlled trial. There were no significant differences in the one and two year actuarial probability of experiencing variceal bleeding between the ISMN group and placebo group. Survival and adverse events were similar in the two groups[25].

ISMN does not reduce the incidence of variceal bleeding in patients with cirrhosis of liver with varices who can not be treated with beta-blockers because of contraindications or intolerance to these drugs, suggesting that ISMN has no place in the prophylaxis of variceal bleeding[25].

Long term effects of propranolol on portal pressure in cirrhotic patients:
Propranolol can prevent the bleeding from esophageal varices and act by reducing the portal inflow due to splanchnic vasodilatation.53 patients with esophageal varices with portal hypertension were treated with propranolol and followed up for three years.Abdominal ultrasonography and Doppler of portal venous system were performed in all subjects.The ultrasonographic parameters were measured before and after a 3-year treatment with propranolol.The patients also underwent endoscopy for evaluation of esophageal varices at the beginning and at the end of the study. Propranolol reduced the portal blood inflow and size of the esophageal varices and the incidence of hemorrhages by variceal rupture was very low in these group of patients[34].

Adding ISMN to beta-blockers to all patients with varices: Is it rational ?
In one randomized study the authors treated 34 patients with cirrhosis and portal hypertension with propranolol and measured HVPG after a median of 4 days. Target HVPG reductions were achieved in 13 responders. ISMN was added in the 21 non-responders and HVPG measured again.7 more patients achieved target HVPG reduction. Rebleeding rates were lower in responders than in non-responders (10% versus 64%). The authors recommended adding ISMN to propranolol or nadolol in individual non-responders, but this requires measurement of the haemodynamic response in every patient. In another randomized study in China 76 cirrhotic patients with variceal bleeding were randomly assigned to treatment with propranolol plus ISMN (34 patients) and propranolol alone (32 patients).7 patients in the propranolol and ISMN group and 13 patients in the propranolol group had rebleeding during the one year

Prevention of Variceal Bleeding : Current Concepts S Perveen et al

after randomization.These results suggest that the addition of ISMN improves the efficacy of propranolol alone in the prevention of variceal rebleeding in cirrhotic patients[35].

Assessment of HVPG response will provide strong prognostic informations since responders on HVPG criteria do better than non-responders. This assessment should be done early preferably within 1-2 weeks of starting treatment because the risk of rebleeding is especially high during the first 6 weeks after the index haemorrhage. Others recommend adding ISMN in all patients thus obviating the need to assess HVPG response. This idea seems reasonable in a high risk situation, such as the prevention of recurrent bleeding[1,36,37].

Endoscopic injection sclerotherapy(EIS):
Endoscopic injection sclerotherapy reduces the risk of recurrent esophageal variceal bleeding from approximately 65 percent to between 30-35 percent at one year but it does not appear to reduce overall mortality.Sclerotherapy is performed every 10 to 14 days until the varices are eradicated,which usually takes five or six sessions.A meta-analysis of nine trials found sclerotherapy and beta-blockers to be equivalent with respect to the risk of recurrent bleeding and the rate of survival.Moreover combination of pharmacotherapy (beta-blockers and ISMN) is superior to sclerotherapy alone in patients with Child-Pugh class A or B cirrhosis[9].Combined sclerotherapy and beta-blockers led to a lower incidence of recurrent bleeding than beta blockers alone without any overall survival benefit[9].

Endoscopic Band Ligation (EBL):
Endoscopic injection sclerotherapy(EIS) has been replaced by Endoscopic band ligation (EBL) which is safer and more effective. EBL is highly effective in obliterating varices. Ligation is associated with a lower risk of recurrent bleeding than sclerotherapy, approximately 25% versus 30% at one year, fewer complications, lower overall cost and higher rates of survival. Therefore, EBL should be considered as standard therapy for secondary prophylaxis. EBL combined with the pharmacological treatment may be more effective than either form of treatment alone. Although the addition of sclerotherapy to ligation may theoretically offer greater protection against recurrent bleeding,this combination does not appear to be advantageous[24,39,40].

Argon plasma coagulation has been used as supplemental treatment for eradication of varices and for prevention of variceal recurrence. Argon plasma coagulation along with EBL was compared with EBL in one recently published series. Mean follow up period was 16 months. No recurrence of varices or variceal hemorrhage was observed in the argon plasma coagualtion group, whereas varices recurred in 42.8% of the patients treated with EBL alone. Argon plasma coagulation of the distal esophageal mucosa after EBL is safe and effective for reducing the rate of variceal recurrence[41].

Transjugular intrahepatic portosystemic shunt (TIPS):
Transjugular intrahepatic portosystemic shunt (TIPS) has become widely accepted worldwide as a percutaneous interventional procedure for treating complications of portal hypertension.An experienced skillful team, however, is necessary to ensure the high technical success of TIPS and to avoid its potential procedural complications.Presently, TIPS is used mainly for treatment of acute or recurrent hemorrhage from gastroesophageal varices refractory to endoscopic therapy.Randomized trials have shown that it is more effective than endoscopic treatment for preventing rebleeding;however, it is associated with a higher incidence of encephalopathy. Both treatments produce comparable survival rates. The cumulative risk of recurrence of bleeding after TIPS is 8 to 18% at one year[9,42,43].

In comparison with surgical shunts, TIPS is a significantly less invasive procedure that can be done in poor surgical candidates with advanced cirrhosis. The high rate of shunt obstructions seen with TIPS mandates close surveillance and maintenance, rendering TIPS a multistage procedure. This is a major disadvantage of TIPS compared to surgery. Stenosis and dysfunction of the shunt after TIPS represent an important complication; the reported rates are 31% at one year and 47% at two years. Presently, both TIPS and surgical shunts have their place in the treatment of gastroesophageal variceal hemorrhage unresponsive to endoscopioc therapy.

Journal of Bangladesh College of Physicians and Surgeons Vol. 22, No. 1, January 2004

TIPS is most suited for class B and C patients, particularly who are candidates for liver transplantation[1,9,44,45].

Surgical treatment:

Decompressive surgical shunts, including nonselective and selective shunts are preferred for patients who are noncompliant with medical or endoscopic therapy and for those who are not candidates for liver transplantation. Although shunts are effective in eradicating varices and preventing recurrent bleeding, they are associated with important operative and post operative complications. Selective shunts are slightly less effective in achieving portal decompression but typically preserve liver function more effectively than nonselective shunts and do not adversely affect the potential for future liver transplantation. Elective surgical therapy is largely reserved for patient with Child-Pugh class A or B cirrhosis[1,42].

Commonly used shunts include the distal splenorenal shunt (DSRS) and the low-diameter mesocaval or portocaval interposition shunt. Rates of recurrent bleeding range from 10 to 20%,with the highest risk occurring during the first month after surgery. Devascularization procedures eg.esophageal transection and devascularization are usually considered in patients who can not receive shunts because of splanchnic venous thrombosis and should be performed by experienced surgeons[9].

Assuming that appropriate surgical expertise is available, the choice of surgical therapy should be individualized and must take into account the severity of the liver disease, patient's compliance and the likelihood of progressive liver dysfunction.

Pharmacotherapy versus EBL:

David Patch and colleagues randomized 102 patients surviving a variceal bleeding to EBL or drug therapy with propranolol with the addition of ISMN if target reductions in portal pressure (evaluated by the HVPG) were not achieved at three months. Overall, results of drug therapy were similar to those of EBL, 44% versus 54% rebleeding rate at one year. There was no differences in survival or non-bleeding complications[46]. Villanueva and colleagues randomly assigned 144 patients with cirrhosis who were hospitalized with esophageal bleeding to receive treatment with EBL (72 patients) or the combined medical therapy with nadolol and ISMN (72 patients).The median follow-up period was 21 months. Thirty patients in the EBL group died, as did 23 patients in medical group. The probability of recurrent bleeding was lower in the medically treated group. Combined therapy with nadolol and ISMN is more effective than EBL for the prevention of recurrent bleeding and associated with a lower rate of major complications. Overall survival rate is also higher in the medically treated group[47]. Lui and colleagues recruited 172 patients with cirrhosis with grade II or III esophageal varices that had never bled. Forty four patients were treated with EBL,66 were treated with propranolol and 62 patients were assigned to ISMN therapy. All the patients were followed up for six years. Variceal bleeding occurred in 7% of patients in EBL group,14% in propranolol group and 23% in ISMN group. There was no statistically significant differences in mortality rates in the three groups. EBL was equivalent to propranolol and superior to ISMN in preventing variceal bleeding[24].

In one randomized trial 121 patients with cirrhosis with portal hypertension were enrolled to undergo EBL (60 patients) or drug therapy by using nadolol plus ISMN (61 patients). After a median follow up period of 25 months, recurrent variceal bleeding developed in 23 patients in the EBL group and 35 patients in medically treated group. Complications occurred in 17% of the EBL group and in 19% of the medically treated group. Fifteen patients in EBL group and eight patients of the nadolol plus ISMN group died. This trial showed that EBL was more effective than nadolol plus ISMN in the prevention of variceal bleeding, with similar complications in both treatment modalities. However, EBL failed to improve overall survival[48].

EIS versus no treatment for the prevention of variceal bleeding:

Since esophageal variceal bleeding is associated with a high mortality rate, prevention of bleeding, might be expected to result in improved survival. Few trials to evaluate prophylactic sclerotherapy found a marked beneficial effect of prophylactic

treatment. These results, however, were not generally accepted because of methodological aspects and because of the reported incidence of bleeding in control group was considered unusually high. In a recently conducted trial 166 patients with esophageal varices were randomized to groups receiving EIS (84 patients) or no specific treatment (82 patients).Primary end points were incidence of bleeding and mortality. During the 32 months of follow up variceal bleeding occurred in 25% of the patients of the EIS group and in 28% of the control group. The one year survival was 87% for the EIS group and 84% for the control group. The three year survival rate was 62% for each group. Complications were comparable for the two groups. In this trial, prophylactic EIS did not reduce the incidence of bleeding from varices in patients with cirrhosis and overall survival was not affected. Meta analysis of a large number of trials showed that the effect of prophylactic EIS is significantly related to the baseline bleeding risk. The effect of prophylactic EIS seems dependent on the underlying bleeding risk. A beneficial effect can only be expected for patients with a high risk of bleeding[49].

Combined EBL and EIS versus EBL alone- a meta analysis:

EBL has been shown to be superior to EIS in prevention of rebleeding and improving survival in patients with cirrhosis. However 25% of patients will rebleed before completion of treatment. A number of trials have compared the combination treatment to EBL alone in achieving rapid and complete eradication of esophageal varices with conflicting results. Meta analysis of seven randomized controlled trials that compared EBL plus EIS with EBL alone showed no overall benefit of combined treatment over EBL alone.No significant difference was seen in cessation of actively bleeding varices, variceal rebleeding and mortality. A significantly higher incidence of esophageal stricture was seen in combination therapy.The combination of EBL and EIS offer no advantage over EBL alone in prevention of rebleeding and in reduction of mortality. It is also associated with a higher complication rate of esophageal stricture[50,51].

EBL plus propranolol versus TIPS:

After a first variceal bleeding episode in patients with cirrhosis of liver, treatment with TIPS and EBL plus propranolol were compared with regard to prevention of variceal rebleeding, complications and mortality. Eighty five patients were randomly allocated to receive TIPS or EBL.The mean observation period was 4.1 years in the TIPS group and 3.6 years in the EBL group. Rebleeding rate was higher in the EBL group (29.9%) than in the TIPS group (19.4%), but the difference was not statistically significant. The probability of survival was similar in both groups (TIPS group 75.9%, EBL group 82.2%). Hepatic encephalopathy was observed more often in the TIPS group (40.5%) than in the EBL group (20.5%)[52].

In view of its good efficacy and the lower cost of treatment, EBL plus propranolol may be recommended as initial procedure for prevention of recurrent variceal hemorrhage,whereas TIPS seems to be the preferable procedure in patients with recurrent bleeding inspite of getting treatment with EBL plus propranolol.

TIPS as first-line therapy:

Cirrhotic patients who survive an episode of acute variceal hemorrhage are at high risk of recurrent bleeding. Many treatments have been found to be effective in preventing rebleeding. Jalan et al compared three cohorts of patients with cirrhosis after index variceal bleeding and found a lower rebleeding rate in patients receiving TIPS (16.2%) compared to either EBL (39.3%) or EIS (74.6%). Despite the efficacy of TIPS in preventing variceal rebleeding, there was no significant difference in survival between the three groups[53].

In another study, TIPS was compared with EBL in the prophylaxis of variceal rebleeding in patients with cirrhosis of the liver. Mean follow up was two years. Mortality risk at two years of follow up was 19.9% in the TIPS group and 16.5% in the EBL group respectively. Probability of remaining free from rebleeding was 83.7% in the TIPS group and 83.9% in the EBL group. Hepatic encephalopathy was more common in the TIPS group than in the EBL group[16].

TIPS is not superior to EBL in the prevention of variceal rebleeding. Furthermore, similar mortality

Journal of Bangladesh College of Physicians and Surgeons Vol. 22, No. 1, January 2004

rates in patients treated with TIPS or EBL negate TIPS as the preferred strategy for prevention of variceal rebleeding.

Prevention of variceal bleeding; Current concepts:
Variceal bleeding is the result of portal hypertension, which is a major complication of liver cirrhosis and carries a high mortality rate. Because of the mortality associated with variceal bleeding,strategies for prevention of the first bleed is important.Risk stratification is important in determining those at risk of bleeding from varices and current data suggest that patients with large varices with red signs, severe underlying liver disease and those who have a HVPG of greater than 12 mm of Hg are at high risk of bleeding. Surveillance for varices in patients with cirrhosis is therefore important. The current first choice treatment is non-selective beta-blockers; which is cheap, easy to administer and reduces the risk of variceal bleeding significantly. Combination of beta-blockers and nitrates looks promising but needs further evaluation. EBL compares favourably with non-selective beta-blockers in preventing the first bleeding episodes in cirrhotic patients and may be an alternative for patients who can not tolerate or have contraindications to beta-blockers. EBL is showed to be superior to EIS in preventing variceal rebleeding.

EIS, EBL or drugs are the standard treatments for the prevention of variceal rebleeding. Failure of this treatment indicates the need for rescue TIPS implantation. The current practice to use EBL as first line and TIPS as second line of treatment is however, not based on evidence since in unselected patients, both treatments have a comparable survival[54].

The role of monitoring HVPG in those being treated with pharmacological agents, the role of newer drugs such as non-selective beta-blockers with intrinsic alpha-adrenergic activity and angiotensin receptor blockers require further evaluation.

Variceal bleeding: much to learn, much to explore:

The newer diagnostic and therapeutic options continue to evolve and important developments have been made in the field of variceal bleeding and portal hypertension. A meeting was held at Baveno to update consensus on different terminologies in relation to portal hypertension. Beta-blockers continue to be the mainstay for primary prophylaxis of variceal bleeding and EBL is fast emerging as a strong contender. EBL is superior to EIS for obliteration of esophageal varices. For gastric varices cyanoacrylate glue continues to be the first line treatment and band ligation is being assessed further. Endosonography has developed strongly in the assessment of variceal eradication and prediction of variceal recurrence. TIPS significantly reduces rebleeding compared to EBL[55]. TIPS and surgical shunts have their place in the treatment of gastroesophageal variceal hemorrhage unresponsive to endoscopic therapy.TIPS is most suited for class B and C patients, particularly those who are candidates for liver transplantation. Surgical shunts should be considered for patients with well preserved liver function.

Conclusion :
Variceal hemorrhage is a common and devastating complication of portal hypertension and is a leading cause of disability and death in patients with cirrhosis. Although the role of endoscopic band ligation in primary prophylaxis is well established, treatment with beta-blockers is well accepted. Because there is a high risk of recurrence after an initial hemorrhage, preventive strategies are required and should be tailored to the patient's clinical condition, surgical risk and prognosis. Drug therapy is a safe and simple way to prevent variceal rebleeding, provided target reductions in HVPG are achieved. Future steps forward include the development of non-invasive ways to assess the hemodynamic response so that therapy can be tailored not only in research studies but also in clinical practice. Unless HVPG measurement is available, physicians will have to make decisions based on published results with a given treatment or combination. In the long term, it is hoped that more effective drugs or drug combinations will be available and that measuring the haemodynamic response will become unnecessary.

References :

1. Bosch J, Garcia-Pagin JC. Prevention of variceal bleeding. Lancet 2003; 361 : 952-54.

2. Saab S, DeRosa V, Nieto J et al. Costs and clinical outcomes of primary prophylaxis of variceal bleeding in

patients with hepatic cirrhosis:a decisison analytic model. Am J Gastroenterol 2003; 98 :763-70.

3 Abraldes JG, Tarantino I, Turnes J et al. Hemodynamic response to pharmacological treatment of portal hypertension and long-term prognosis of cirrhosis. Hepatology 2003; 37 : 902-8.

4. Seewald S, Mendoza G, Seitz U et al. Variceal bleeding and portal hypertension:has there been any progress in the last 12 months. Endoscopy 2003; 35 : 136-44.

5. Rubenstein JH, Inadomi JM. Empiric beta-blockers for the prophylaxis of variceal hemorrhage:cost effective or clinically applicable. Heaptology 2003; 37 : 249-52.

6. Brensing KA, Horsch M, Textor J et al. Hemodynamic effects of propranolol and nitrates in cirrhosis and transjugular intarhepatic portosystemic stent-shunt. Scand J Gastroenterol 2002;37:1070-6.

7. Maldonado D, Barkin JS. Combined therapy for secondary prophylaxis of variceal rebleeding? Am J Gastroenterol 2002; 97 : 2134-6.

8. De BK, Bandyopadhyay K, Das TK et al. Portal pressure response to losartan compared with propranolol in patients with cirrhosis. Am J Gastroenterol 2003; 98 : 1222-24.

9. Sharma AI, Rockey DC. Gastroesophageal variceal hemorrhage. N Engl J Med 2001; 345 : 669-81.

10. Kovacs TO, Jensen DM. Endoscopic treatment of acute esophageal variceal bleeding. Drugs Today 2000; 36 : 339-53.

11. Wu JC, Sung JJ. Update on treatment of variceal hemorrhage. Dig Dis 2002; 20 : 134-44.

12. Spigel BM, Targownik L, Dulai GS et al. Endoscopic screening for esophageal varices in cirrhosis:is it ever cost effective. Heaptology 2003; 37 : 366-77.

13. Wu YK, Wang YH, Tsai CH et al. Modified Hasssab procedure in the management of bleeding esophageal varices- a two year experience. Heaptogastroenterology 2002; 49 : 205-7.

14. Yachha SK, Chetri K, Lal R. Management of portal hypertension. Indian J Pediatr. 2002; 69 : 809-13.

15. Novick DM. Prevention of recurrent variceal bleeding. N Engl J Med 2001; 345 : 209-10.

16. Gulberg V, Schepke M, Geigenberger G et al. Transjugular intrahepatic portosystemic shunting is not superior to endoscopic variceal band ligation for prevention of variceal rebleeding in cirrhotic patients:a randomized, controlled trial. Scand J Gastroenterol 2002; 37 : 249-52.

17. Rossle M, Siegerstetter V, Olschewski M et al. How much reduction in portal pressure is necessary to prevent variceal rebleeding ?A longitudinal study in 225 patients with transjugular intrahepatic portosystemic shunts. Am J Gastroenterol 2001; 96 : 3379-83.

18. Luketic VA. Management of portal hypertension after variceal hemorrhage. Clin Liver Dis 2001; 5 : 677-707.

19. Lowe RC,Grace ND. Primary prophylaxis of variceal hemorrhage. Clin Liver Dis 2001; 5 : 665-76.

20. Gracia-Pagan JC. Non-selective beta-blockers in the prevention of first variceal bleeding. Is there any definite alternative? J Hepatol 2002; 37 : 315-21.

21. Chung S. Management of bleeding in the cirrhotic patient. J Gastroenterol Hepatol 2003; 18 : 112-4.

22. Abraczinskas DR, Ookubo R, Grace ND et al. Propranolol for the prevention of first variceal hemorrhage:a lifetime commitment. Rev Gastroenterol Disord 2002; 2 : 143-5.

23. Gracia-Pagan JC, Morillas R, Banares R et al. Propranolol plus palcebo versus propranolol plus isosorbide-5-mononitrate in the prevention of a first variceal bleed:a double-blind RCT. Hepatology 2003; 37 : 1254-6.

24. Lui HF, Stanley AJ, Forrest EH et al. Primary prophylaxis of variceal hemorrhage:a randomized controlled trial comparing band ligation, propranolol, and isosorbide mononitrate. Gastroenterology 2003; 124 : 2005.

25. Gracis-Pagan JC, Villanueva C, Vila MC et al. Isosorbide mononitrate in the prevention of first variceal bleed in patients who cannot receive beta-blockers. Rev Gastroenterol 2001; 2 : 143-5.

26. Teres J, Bosch J, Bordas JM et al. Propranolol versus sclerotherapy in preventing variceal rebleeding: a randomized controlled trial. Gastroenterology 1993; 105 : 1508-14.

27. Abecasis R, Kravetz D, Fassio E et al. Nadolol plus spirolactone in the prophylaxis of first variceal bleed in nonascitic cirrhotic patients:A preliminary study. Hepatology 2003; 37 : 359-65.

28. Marrero JA, Scheiman JM. Prevention of recurrent variceal bleeding:as easy as A. P. C. Gastrointest Endosc 2002; 56 : 467-71.

28. Post AB. Cost effectiveness of preventing variceal hemorrhage. Heapatology 2003; 37 : 366-77.

30. Garcia NJ, Sanyal AJ . Portal hypertension. Clin Liver Dis 2001; 5 : 509-40.

31. McCormick PA, O'Keefe C. Improving prognosis following a first variceal haemorrhage over four decades. Gut 2001; 49 : 607-8.

32. Arguedas MR, Heudebert GR, Eloubeidi MA et al. Cost-effectiveness of screening, surveillance and primary prophylaxis strategies for esophageal varices. Am J Gastroenterol 2002; 97 : 2441-52.

33. Kowdley KV. Motion-prophylactic banding of esophageal varices is useful:arguments against the motion. Can J Gastroenterol 2002; 16 : 693-5.

34. Orban-Schiopu AM, Popescu CR. Long term effects of propranolol on portal pressure in cirrhotic patients. Rom J Gastroenterol 2003; 12 : 25-30.

35. Bureau C, Peron JM, Alric L et al. Treatment of portal hypertension:adapting medical therapy to hemodynamic response for the prevention of bleeding. Hepatology 2002; 36 :1361-66.

36. Bosch J. Improving pharmacologic therapy of portal hypertension. Hepatology 2002; 36 : 1330-32.

37. Bosch J, Gracia-Pagan JC. Complications of cirrhosis: portal hypertension. J Hepatol 2000; 32 : 141-56.

38. Lo GH, Lai KH, Cheng JS 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 : 461-65.

39. Yol S, Belviranli M, Toprak S et al. Endoscopic clipping versus band ligation in the management of bleeding esophageal varices. Surg Endosc 2003; 17 : 38-42.

40. Bratovic I, Lacevic N. Management of esophageal varices. Med Arch 2002; 56 : 11-12.

41. Cipolletta L, Bianco MA, Rotondano G et al. Argon plasma coagulation prevents recurrence after band ligation of esophageal varices:preliminary results of a prospective randomized trial. Gastrointest Endosc 2002; 56 : 467-71.

42. Rosch J, Keller FS. Transjugular intrahepatic portosystemic shunt:present status, comparison with endoscopic therapy and shunt surgery, and future prospectives. World J Surg 2001; 25 : 337-45.

43. Said A, Safdar N, Lucey M. Is TIPS a cost-effective therapy for the prevention of variceal rebleeding ? Hepatology 2002; 36 : 259-60.

44, Zucker SD. Some TIPS for the prevention of recurrent variceal hemorrhage. Gastroenterology 2002; 123 : 384-6.

45. Escorsell A, Banares R, Gracia-Pagan JC et al. TIPS versus drug therapy in preventing variceal rebleeding in advanced cirrhosis: a randomized controlled trial. Hepatology 2002; 35 : 385-92.

46. Patch D, Sabin CA, Goulis J et al. A randomized controlled trial of medical therapy versus endoscopic ligation for the prevention of variceal rebleeding in patients with cirrhosis. Gastroenterology 2002; 123 : 1013-19.

47. Villanueva C, Minana J, Ortiz J et al. Endoscopic ligation compared with combined treatment with nadolol and isosorbide mononitrate to prevent recurrent variceal bleeding. N Engl J Med 2001; 345 : 647-55.

48. Lo GH, Chen WC, Chen MH et al. Banding ligation versus nadolol and isosorbide mononitrate for the prevention of esophageal variceal rebleeding. Gastroenterology 2002; 123 : 728-34.

49. Van Buuren HR,Rasch MC, Batenburgh PL et al. Endoscopic sclerotherpay compared with no specific treatment for the primary prevention of bleeding from esophageal varices. A randomized controlled multicentre trial. Gastroenterol 2003; 15 : 22-24.

50. Singh P, Pooran N, Indaram A et al.Combined ligation and sclerotherapy versus ligation alone for secondary prophylaxis of esophageal variceal bleeding:a meta-analysis. Am J Gastroenterol 2002; 97 : 623-29.

51. Vargas L, Morales X, Ovalle L et al. Endoscopic ligation plus sclerotherapy in esophageal varices treatment. Experience in active bleeding and in the elective treatment. Rev Med Chil 2001; 129 : 1387-94.

52. Sauer P, Hansmann J, Richter GM et al. Endoscopic variceal ligation plus propranolol vs. trnasjugular intrahepatic portosystemic stent shunt:a long-term randomized trial. Endoscopy 2002; 34 : 690-7.

53. Harrison P, Karani J. Secondary prophylaxis of esopahgeal variceal hemorrhage: a role for transjugular intrahepatic portosystemic shunt? Eur J Gastroenterol 2002; 14 : 591-3.

54. Rossle M. Prevention of rebleeding from oesophageal-gastric varices. Eur J Gastroenterol 2001; 13 : 343-8.

55. Bhasin DK, Malhi NJ. Variceal bleeding and portal hypertension:much to learn, much to explore. Endoscopy 2002; 34 : 119-28.