# Prophylaxis of first variceal bleeding

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Almost all patients with chronic liver disease will develop portal hypertension. The main clinical complications of portal hypertension are ascites formation and its sequelae, porta systemic shunting with hepatic encephalopathy and gastro-oesophageal varices formation with bleeding. Variceal bleeding accounts for 10 to 30% of all cases of upper gastro-intestinal haemorrhage (1). Variceal bleeding occurs in 25 to 35% of patients with cirrhosis and accounts for 75 to 90% of bleeding episodes in these patients (2,3). The mortality rate of first variceal haemorrhage remains high (20-35%) in spite of significant improvements in treatment and is associated with a high hospital cost (4,5). Therefore prevention of bleeding is still the way to go.

## 1. Screening

a. *Who to screen :*

If one wants to prevent variceal bleeding, one has to screen. All cirrhotic patients should be screened for the presence of gastro-oesophageal varices at the time of the initial diagnosis of cirrhosis (6). In case of decompensated cirrhosis, varices are present in 60% of the patients and in 30% of compensated cirrhotic patients (7).

In patients with chronic liver diseases under follow-up, platelet count may have a potential use in the screening for varices (8). In a case control study in patients referred for liver transplantation, a platelet count of 80 3 $10^9$/L or less was an independent risk factor for large varices (OR, 2.3 ; 95%CI, 1.4-3.9) (9).

b. *When to rescreen :*

Two large studies investigated the development and progression of gastro-oesophageal varices. The increase in the incidence of varices was nearly 5% per year. Based on the likelihood that newly appearing varices in compensated patients are small (low risk of bleeding), it is recommended that in patients with compensated cirrhosis without varices, screening has to be performed every 2-3 years (6).

Five studies assessed the interval of progression from small to large varices. They showed variable rates of progression in 8% to 30% per year. As such in general, one could expect to find progression of varices in approximately 10% of the patients per year in the first two years following diagnosis of the varices. Therefore, in compensated cirrhotic patients with small oesophageal varices, endoscopy should be repeated at 1-2 years intervals to evaluate the progression of varices. Once large varices are detected, there is no further indication for subsequent evaluation (6).

## 2. Assessment of risk of bleeding

Although variceal bleeding is a common complication of cirrhosis, not all patients will bleed. Variceal bleeding occurs in approximately 24% at two years follow-up and with prolonged follow-up in about 30-40% of cirrhotics (10). It means that at least half of the patients with cirrhosis will never develop an episode of variceal bleeding. Therefore, primary prevention should be offered to those with the highest probability of bleeding.

Prospective studies have shown that certain factors are associated with the risk of the first gastrointestinal haemorrhage in patients with cirrhosis and thus may be used to identify candidates for prophylactic treatment. Approximately 25% of cirrhotics screened will be in the high-risk category (10,11).

The main risk factor of a first variceal bleeding is the size of the varices. The most reproducible way to estimate the size of varices is to divide them in small and large varices, small varices measuring less than 5 mm (i.e. the size of an open forceps). Other commonly used risk factors are the presence at endoscopy of red colour signs and the severity of liver disease expressed as the Child Pugh score (2). An increased risk of variceal bleeding is also associated with the level of variceal pressure (12,13) and the portal flow and a reduction in the congestive index of the portal vein (14). The level of hepatic vein pressure gradient (HVPG) does not correlate well with risk of bleeding.

The main limitation of the available prognostic indices is that they can only identify a relatively small proportion of patients who will eventually bleed. In the NIEC study for example, 20% of the bleedings occurred

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in patients classified as low risk (10). A strategy to treat all patients with varices eliminates the need to repeat an endoscopy and would cover also this subgroup of patients with calculated low risk who will nevertheless bleed.

## 3. Pre-primary prevention of variceal bleeding

Studies in experimental models of cirrhosis have shown that propranolol, administered in the early stages of the portal hypertensive process, prevents the development of porto-systemic collaterals. Whether propranolol can prevent the development of varices in humans with cirrhosis was first explored in a French study (15). This study included patients without and patients with small gastro-oesophageal varices. ß-blockers could not prevent the development of large varices. Another study is in progress. At present, ß-blockers cannot be recommended to prevent the development of large oesophageal varices.

## 4. Treatment with ß-blockers

Non-selective ß-blockers reduce portal pressure and consequently variceal pressure and as such the risk of variceal bleeding by decreasing splanchnic flow. This occurs as a reflex splanchnic arterial constriction due to unopposed alpha 1-adrenergic vasoconstriction as well as a reduction of the cardiac output, mainly due to beta 1-adrenergic blockade.

Multiple studies have shown that ß-blockers reduce the risk of bleeding and the results of meta-analyses are consistent (16,17). In patients with large varices, propranolol or nadolol reduced, after a mean follow-up of 2 years, the bleeding rate of 25% in the control groups to 15%. At two years, ß-blockers significantly reduced the relative risk of first variceal bleeding by approximately 50% and this was associated with a reduction in bleeding-related death.

These results were observed whatever the cause and the severity of cirrhosis. The efficacy was even more marked in patients with liver dysfunction or in patients with ascites. Although an effect was also noted in patients with small varices, this did not reach statistical significance.

The dose of ß-blockers is titrated in order to achieve a heart rate of 55 beats per minutes or a reduction of 25% from the baseline rate. Propranolol should be administered twice a day and must include an evening dose ; bleeding from varices occur frequently during the night which can be explained by the circadian variation in portal hypertension (18).

The use of ß-blockers in case of cirrhosis and large varices is precluded in 15-20% of the patients due to contraindications for ß-blockers and in 5-10% of the eligible patients discontinuation of treatment was required in long-term follow-up.

Several studies have shown that the risk of variceal bleeding is highest during the first year after the diagnosis of varices. It was therefore proposed that ß-blockers are probably only necessary during this high risk period. A recent study, however, showed that in patients tapered off of propranolol the protective effect of propranolol against variceal haemorrhage was no longer present and the risk of bleeding returned to what would be expected as in an untreated population. Patients who discontinued ß-blockers experience increased mortality compared with an untreated population (19). This observation supports the idea of indefinite treatment.

## 5. Treatment with nitrates

Isosorbide-5-mononitrate (Is-5-Mn) is preferred to shorter acting dinitrated compounds because it has no hepatic metabolism and does not accumulate in patients with cirrhosis (20). Is-5-Mn reduces portal hypertension by a decrease in splanchnic flow caused by a baroreflex mediated splachnic arterial vasoconstriction and by a decrease in portal collateral vascular resistence and probably also by a reduction in intrahepatic resistance. However, the exact mechanism of action is still unclear. Headaches and arterial hypotension which predominantly occur after the first few doses are the main side effects of Is-5-Mn, but the major problem is that nitrates accentuate the systemic haemodynamic disturbances i.e. arteriolar dilatation seen in case of portal hypertension.

a. *Combination therapy with ß-blockers :*

Three studies have been reported that combination was more effective (21,22,23) and a meta-analyis of these three studies including 552 patients (17), reveals an overall bleeding rate of 10% in the combination therapy versus 15% in the patients only treated with non-selective ß-blockers. Mortality was similar in both treatment schedules (10%) but side effects were more frequent with combination therapy.

b. *Prophylactic monotherapy with nitrates :*

The effect of nitrates in the primary prevention of variceal bleeding is inferior to ß-blockers and has more side-effects such as hypotension and sodium retention in patients with ascites. In one trial Is-5-Mn was found to be an alternative treatment of propranolol but at 5 years the mortality rate in patients older than 50 receiving nitrates was significantly greater than with propranolol (24). In a recent study of patients with a contraindication or intolerance of ß-blockers, Is-5-Mn did not reduce the incidence of variceal bleeding in comparison with placebo (25). Thus, nitrates as single therapy does not seem indicated for the prevention of the first variceal bleeding in patient with cirrhosis.

## 6. Assessment of efficiency : monitoring of pharmacologic treatment

Changes in hepatic venous pressure gradient have been used to predict the response of drug protection on variceal bleeding or rebleeding. A decrease in HVPG below 12 mmHg seems to guarantee a good prevention of bleeding. However, such level is only obtained in a limited number of patients.

It has been suggested that in case a reduction of 20% of the original HVPG is reached, the risk of rebleeding is also reduced (26,27). The value of this measurement in case of primary prophylaxis has been demonstrated in one study (28).

The relationship between a reduction in HVPG and clinical response of bleeding is however complex, certainly since the HVPG value is not directly related to the risk of bleeding (29).

In addition, hepatic venous pressure measurements can only be used in case of cirrhosis since it underestimates portal pressure in patients with presinusoidal portal hypertension. Furthermore, it is yet unclear when a repeat measurement should be performed.

The level of variceal pressure correlates well with the risk of bleeding and non selective ß-blockers reduce the level of variceal pressure (30). In a prospective cohort study we found that in patients with large varices and cirrhosis of which a group was treated with propranolol, the bleeding rate was reduced in case variceal pressure was reduced to below 15 mmHg (12). Similar as with HVPG measurement a reduction of variceal pressure of 20% or more is associated with a lower risk of bleeding or rebleeding (31). Studies with variceal pressure measurement to follow up the effect of therapy seem very attractive but widespread use was hampered until recently because approved devices for variceal pressure measurement were not available. Prospective studies using variceal pressure as a method to guide pharmacological or endoscopic treatment, are further needed.

## 7. Endotherapy in the primary prevention of variceal bleeding

Several studies have compared endoscopic sclerotherapy with endoscopic variceal ligation. Both techniques obtained a high variceal obliteration rate > 90% but the number of endoscopic sessions required has been fewer with ligation and this technique carried also a lower rate of complications. Ligation seems thus the treatment of choice if one would use endotherapy for prophylactic treatment.

Variceal ligation has been compared to ß-blockers in patients with large oesophageal varices in 4 studies. Among 283 subjects from 4 trials, the relative risk of first variceal bleeding was 0.48 (0.2-0.96) ; however, there was no effect on either bleed-related mortality or all-cause mortality (32).

Although variceal ligation being more expensive, patients with large gastro-oesophageal varices with intolerance to ß-blockers or unresponsible to combination therapy are probably good candidates for preventive endotherapy. However, this indication still has to be proven.

## 8. Primary prevention of bleeding of gastric varices

The overall prevalence of gastric varices varies between different studies and ranges from 10 to 50%. When compared with oesophageal varices, gastric varices bear a higher morbidity in patients with cirrhosis. Fundic varices bleed more frequently than varices involving the lesser curvature of the stomach.

The prevention of the first bleeding episode for gastric and ectopic varices in patients with cirrhosis and the prevention of variceal bleeding in patients with extrahepatic portal hypertension is still not been evaluated in prospective trials. ß-blockers may be used since they reduce portal and variceal pressure.

Conclusions and future prespectives

In spite of significant improvements in treatment, the mortality of a first variceal haemorrhage in patients with cirrhosis remains high. The best way to avoid this, is prevention. Therefore all cirrhotic patients should be screened for the presence of varices at the time of the initial diagnosis of cirrhosis. In compensated cirrhotic patients without varices, screening by gastrointestinal endoscopy has to be performed every 2-3 years. In patients with small varices, endoscopic screening has to be performed after 1-2 years. In patients with chronic liver disease under follow-up, platelet count may be helpful. Since a platelet count of 80 x $10^9$/L or less is indicative for the presence of large varices. Variceal size is the main validated factor to assess the risk of a first variceal bleeding. The present prognostic indices still fail to recognize a subgroup of patients classified as low-risk who will bleed. Variceal pressure is closely related with the risk of variceal rupture. The value of variceal pressure measurement to assess the risk of a first variceal haemorrhage should be further investigated.

Today ß-blockers cannot be recommended for the pre-primary prevention of development of gastro-oesophageal varices in patients, in contrast to what was suggested by studies in rats with portal hypertension. In case of large varices, non-selective ß-blockers such as propranolol and nadolol have to be started and recent data support the idea of indefinite treatment. Data are missing about the primary prevention of variceal bleeding in case of gastric varices. At present there is no indicatation for monotherapy with nitrates. Combination with ß-blockers and nitrates can not be recommended in all patients because of the possible side-effects of nitrates, especially in patients with older age and tense

ascites. Combination therapy should therefore currently be restricted to patients with no response to ß-blockers. The best way to assess this is via haemodynamic monitoring, although the exact methods still have to be clarified.

In case of intolerance or contra-indication for ß-blockers, endoscopic variceal ligation can be performed until variceal obliteration, although this approach has also to be further explored.

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