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REVIEW

Primary Prevention of Bleeding from Oesophageal Varices

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ABSTRACT

Variceal bleeding is the most serious complication of patients with cirrhosis and portal hypertension. Mortality related to variceal bleeding has been falling in recent years but is still considered among the leading causes of death in these patients. Therefore, the issue of primary prophylaxis of variceal bleeding is an important one. In the pre-primary prophylaxis setting (prevention of formation/growth of varices) all cirrhotics should be screened for varices at diagnosis although there is no currently indication for treating patients in order to prevent the formation of varices. Areas requiring further study include the natural history of low-risk varices and treatment possibilities for the decrease or the prevention of the development and/or the progression of varices. Patients with small varices could be treated with beta-blockers, which have been proved effective in reducing the risk of first variceal bleeding in patients with medium and large oesophageal varices. Endoscopic band ligation seems to be more effective in recent trials, but concerns have been raised regarding its safety. Further, studies are required to clarify whether the use of the combination of band ligation and beta-blockers is better than each treatment alone. The future aim is to improve current medical therapy taking into consideration the cost-effectiveness and the quality of life.

KEY WORDS: *esophageal varices, primary prevention, beta-blockers, nitrates, endoscopic sclerotherapy, endoscopic band ligation*

INTRODUCTION

Liver cirrhosis is responsible for 90% of patients with portal hypertension in Europe and North America. Portal hypertension represents the most serious complication of cirrhosis and results in the development of portosystemic shunts comprising esophageal varices [1].

It is considered that one third of cirrhotic patients with esophageal varices will experience the first episode of variceal haemorrhage within one year following the diagnosis of varices. The risk for the first episode of variceal bleeding is higher in patients with severe liver failure, large varices and red spots found endoscopically. Moreover, bleeding-related mortality is extremely high as 30-50% of patients will die within six weeks from the first episode of bleeding [1].

The bad prognosis of variceal bleeding has led to attempts both, to identify patients in high-risk for bleeding and to prevent it. Many different therapies have been assessed over the last 30 years including surgery, administration of drugs (non selective beta-blockers, isosorbide mononitrate or the combination of them) and endoscopic eradication of varices (sclerotherapy or banding ligation).

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NATURAL HISTORY OF VARICES

When cirrhosis is diagnosed, varices are present in 30% of patients with well compensated cirrhosis and 60% of patients with decompensated cirrhosis [2]. After varices are formed their size increases and occasionally they bleed. It has been reported that they increase by 10-20% in the first two years after the first endoscopic observation [1].

In a study by Pagliaro et al, 4% of cirrhotic patients without varices at the first endoscopy, and 25% of patients with small varices developed large varices after a 6 year follow-up. However, in another study by Cales et al, large varices were found in 31% of patients without varices and in 70% of patients with first degree varices at initial endoscopic examination, after a 2 year follow-up. These differences have been attributed to different definitions of the size of varices as well as to the large percentage of active alcoholic abusers included in the French study [3].

PREDICTION OF THE PRESENCE AND DEVELOPMENT OF ESOPHAGEAL VARICES

Many efforts have been made to find clinical parameters that could accurately predict the presence of varices as endoscopy is an invasive procedure and is unnecessary for well-compensated cirrhotics with little probability of having developed varices [4]. A French group has suggested that platelet count and prothrombin index have a diagnostic accuracy of 72% in the prediction of the presence of varices, although their predictive power was suboptimal for clinical use and would not obviate the necessity for screening endoscopy [5]. In another study that enrolled 143 patients with Child Pugh A/B liver cirrhosis - mainly of viral aetiology - the presence of varices was correlated to PT index <70%, platelets <100000/mm3 and ultrasound-determined portal vein diameter >13mm [6].

It is widely accepted that esophageal varices are not formed if portal pressure, indirectly assessed with HVPG (hepatic venous pressure gradient) does not exceed 10 -12 mmHg. Thus, screening for the development of varices could be replaced by HVPG [7]; however not all patients of this group have varices at endoscopic examination.

FOLLOW-UP OF PATIENTS WITH ESOPHAGEAL VARICES

There is no consensus on the optimal intervals for surveillance endoscopy. In an AASLD symposium in 1996 [8], it was suggested that in Child-Pugh A patients endoscopic evaluation should be performed when there are indications of portal hypertension (platelets < 140.000, portal vein diameter >13 mm, and ultrasound indication of collateral blood flow). In Child-Pugh B and C patients endoscopic examination should be performed at the time of diagnosis. Patients without varices should undergo endoscopic examination every 2 years if liver function is stable, or once a year if there are signs of deterioration. As the large varices development rate is higher in patients with small varices at initial endoscopic evaluation than in patients without varices, patients with small varices should undergo endoscopic examination annually. In a recent consensus workshop that was held in Baveno [9], it was proposed that all patients with liver cirrhosis should undergo endoscopic examination at the time of initial diagnosis (See Baveno IV recommendations in Table I).

TABLE 1. Recommendations of the Baveno IV Consensus Workshop on methodology of diagnosis and therapy in portal hypertension.

• all cirrhotics should be screened for varices at diagnosis
• there is no indication for treating patients in order to prevent the formation of varices
• patients with small varices could be treated with non-selective beta-blockers to prevent progression of varices and bleeding, but further studies are needed before formal recommendation on their use can be made
• patients with small varices with red wale signs or of Child-Pugh C class have an increased risk of bleeding and may benefit from treatment
• non selective beta-blockers reduce the risk of first variceal bleeding in patients with medium and large oesophageal varices
• ISMN alone must not be used
• There are not enough data to support the use of the combination of beta-blockers plus ISMN or spironolactone plus beta-blockers
• EBL is useful in preventing variceal bleeding in patients with medium and large varices
• EBL is more effective than non-selective beta-blockers in preventing first variceal bleeding but does not improve survival. However, the long term benefits of EBL are uncertain because of the short duration of follow up
• EBL should be offered to patients with medium/large varices and contraindications or intolerance to beta-blockers.

RISK OF FIRST VARICEAL BLEEDING

It has been postulated that the risk factors of esophageal varices rupture are the advanced liver failure, as assessed with Child - Pugh score, large varices and the presence of red spots at endoscopy. However, the above risk factors were found in only 1/3 of patients with variceal haemorrhage. Therefore, other factors should probably be taken into consideration in the evaluation of variceal haemorrhage risk.

Recently, the interest of hepatologists has been focused on the role of hemodynamic factors in the development and rupture of varices. Some studies have shown that HVPG constitutes an independent risk factor of bleeding and death [10]. Variceal bleeding does not occur if HVPG does not exceed the limit of 12 mmHg. Beyond this limit there is no linear correlation between the likelihood of bleeding and HVPG, although pressure is usually high in patients who bleed. In a recent study, cirrhotic patients under pharmacologic therapy were followed-up for a long period reaching 8 years. It was confirmed that the risk of variceal bleeding is negligible if HVPG decreases by ≥20% or has a value of ≤12 mmHg [11].

It has been suggested that variceal pressure also represents an independent risk factor for the first bleeding episode [12] and an important prognostic factor in patients with portal hypertension of cirrhotic or non-cirrhotic aetiology [13]. It has also been reported that it constitutes a more reliable prognostic indicator of variceal rupture compared to HVPG but its measurement has many technical difficulties and reliability problems. It appears that the combination of clinical, endoscopic and hemodynamic parameters will constitute in the future the most reliable source of information regarding the risk of variceal rupture.

Other potential independent risk factors include the aetiology of cirrhosis, the presence of HCC, the patency of portal and hepatic veins, the direction of portal flow, and the alcohol consumption [3]. Recent studies have focused on the role of bacterial infection as an important factor associated with increased risk of rupture of esophageal varices [14].

PREVENTION OF GROWTH OF ESOPHAGEAL VARICES

PHARMACEUTICAL INTERVENTION

Beta-blockers decrease portal vein pressure in patients with cirrhosis and limit the development of portosystemic shunts in animals with portal hypertension. In a hemodynamic study that was published in 1997, the changes in the portal vein pressure following the administration of non-selective beta-blockers (timolol) was assessed in 50 cirrhotics with or without esophageal varices. Portal pressure was reduced significantly in all patients after timolol administration and reduction was higher in patients without varices supporting that non-selective beta-blockers are more effective if they are administered earlier [15].

However, in a recent study of 213 patients without esophageal varices randomized to receive either timolol (108 patients) or placebo (105 patients), beta-blocker were not effective in the prevention of varices formation. It should be noted that the majority of patients (88%) had Child A liver failure and only 12% Child B. Median follow-up was 4.2 years, while mean daily dose of timolol was 10.8 mg [16].

Another prospective study was designed to investigate the efficacy of propranolol in the prevention of large esophageal varices development in patients with small varices or without varices in the oesophagus; 102 patients received propranolol 160 mg/d and 104 patients received placebo. After a mean follow-up of 2 years, 31% of patients in the propranolol group developed large varices as compared with 14% in the placebo group. The authors concluded that the administration of propranolol is not helpful in the prevention of large varices development. However, it should be emphasized that one third of patients were lost during follow-up [17].

Finally, Mercel et al. recently found that nadolol prevents the progress of small size varices into medium and large size varices and suggested that beta-blocker prophylaxis of variceal bleeding in patients with compensated cirrhosis should be started when small esophageal varices are found in endoscopy [18].

RANDOMIZED TRIALS FOR THE PRIMARY PREVENTION OF VARICEAL BLEEDING

SURGERY VERSUS NO TREATMENT

The efficacy of portocaval shunt surgery in the primary prevention of variceal bleeding as compared to no treatment has been evaluated in 4 studies [3]. The risk of bleeding was lower in patients who underwent surgery but the risk of encephalopathy was significantly increased and survival was significantly worse. Thus, surgery has no place in the primary prevention of variceal haemorrhage today and the advent of liver transplantation removes any rationale for prophylactic surgery of any kind in cirrhotics.

SCLEROTHERAPY VERSUS NO TREATMENT

The efficacy of endoscopic sclerotherapy in managing acute variceal haemorrhage led to its application for the prevention of first variceal bleeding (20 studies - 1756 patients) [3].

In a meta-analysis, Pagliaro L et al [3], suggested that the available data are insufficient to support the use of sclerotherapy in primary prophylaxis. Furthermore, Fardy, et al in another meta-analysis postulated that sclerotherapy cannot

be recommended as routine prophylactic therapy because, although it appears to decrease bleeding risk significantly, it results in a deleterious effect in overall survival.

In a study by Strauss E et al [19] with a median follow-up of 2 years 21 patients were allocated to sclerotherapy and 22 constituted the control group, 5 patients bled in the sclerotherapy group as compared to none in the control group, while mortality was similar in both groups.

Recently, in a randomized study [20] that enrolled 166 patients with II, III, and IV degree esophageal varices and a median follow-up of 32 months, bleeding was observed in 25% of patients allocated to sclerotherapy and in 28% of the control group. There was a three-year survival rate of 62% in both groups. The authors conclude that sclerotherapy did not decrease variceal haemorrhage implications in patients with liver cirrhosis and low or medium bleeding risk. However, although bleeding related mortality decreased, overall mortality did not. Therefore, the beneficial effect of sclerotherapy, if any, was expected only in high risk patients.

LIGATION VERSUS NO TREATMENT

In recent years, endoscopic band ligation (EBL) has replaced sclerotherapy as the method of choice for the management of variceal bleeding. Ligation is at least as effective as sclerotherapy but has fewer complications [21]. Ligation of esophageal varices as compared to no-treatment was evaluated in 4 studies [22-25] that enrolled only high-risk patients.

Lay et al. found that prophylactic band ligation can reduce the incidence of bleeding and death after a median follow-up of 2 years [23]. In the study of Lo et al. although prophylactic band ligation did not decrease bleeding likelihood significantly in cirrhotic patients with large esophageal varices, it proved beneficial for the subgroup of Child-Pugh B patients [24]. Sarin et al. randomized 68 patients, to ligation (n=35) or no-treatment (n=33). 8.6% of patients who underwent ligation and 39.4% who did not receive treatment experienced bleeding after a median follow-up of 14.1 ± 5.0 months. Furthermore, bleeding-related mortality was lower in the group of ligation as compared to that of the control group [25].

Side effects are often reported in the group of patients undergoing band ligation [26]. Retrosternal pain, dysphagia and fever have been observed roughly in 1/3 of patients. Two patients passed away, one because of oesophagial perforation related to the use of overtube [25] and one after bleeding related to oesophageal ulcer following ligation, which was complicated by aspiration [24].

Recently, in a randomized trial [27] EBL was compared to no treatment (NT) in cirrhotics with intolerance or contraindications to b-blockers for prevention of first bleeding. A sample size of 214 was planned with all size varices. However the trial was stopped after assessing 52 patients due to increased bleeding in the EBL group. Baseline severity liver disease and endoscopic features were similar. After a mean follow-up period of 19.5±13.3 months: 5 bled in EBL group (20%), 3 from varices (2 after banding 11 and 17 days; 1 during procedure) and 2 from gastropathy; 2 bled in NT group (7,4% - 2 both varices) (p= 0.24). Deaths: 7 EBL group and 11 NT group (p= 0.39). 60% of the bleeding in the banding group was probably iatrogenic, requiring the study to be stopped. EBL was no better than no-treatment. This is the first study suggesting that EBL may be harmful when used as primary prophylaxis, similar to prophylactic sclerotherapy in the past.

NON SELECTIVE BETA-BLOCKERS VERSUS NO TREATMENT

Non selective beta-blockers are more effective than selective beta-blockers, as b1 activity is important for reducing cardiac flow and b2 activity is mandatory for reducing splanchnic blood flow, inducing splanchnic arterial vasoconstriction [28]; they also decrease blood flow in existing portosystemic shunts. Their favourable effect is achieved in patients with or without ascites and with preserved or poor liver function. They are also potentially effective in the prevention of bleeding from portal gastropathy.

There are 9 prophylactic trials [3] comprising 996 patients; seven of them used propranolol, and two nadolol. There was a statistically significant bleeding risk reduction with b-blockers. 205 episodes of bleeding in 507 patients were reported in the control groups (40.4%), and 146 bleeding episodes in 489 patients receiving treatment (29.9%). 261 deaths in 507 patients were recorded in the control groups (51%), and 211 deaths in 489 patients in the groups receiving treatment (43%). It is estimated that 11 patients should be treated in order to prevent a bleeding episode. If only studies with medium, and large size varices are included, the effectiveness of beta-blockers in the prevention of bleeding is higher and 8 patients need to be treated in order to prevent a bleeding episode. Lastly, treatment with propranolol appears to be cost-effective in all the groups of cirrhotic patients [29].

In a meta-analysis by Poynard et al, including 589 patients that enrolled in 4 randomised studies with medium or large size varices (4 to 6 mm, or second degree or occupying more than 1/3 of the oesophageal lumen), 286 received beta-blockers (203 propranolol, and 83 nadolol) and 303 received placebo. Two years later, the percentage of patients who did not bleed was 78 ± 3% in the group who received beta-blockers and 65 ± 3% in the placebo group (p = 0.002). Two year survival rate was 71 ± 3% in the group that received treatment and 68 ± 3% in the control group (p = 0.34). If age and severity of liver failure were taken into account, survival was better in the group that received treatment (p = 0.09). Both, propranolol and nadolol were effective in preventing the first bleeding-episode. The authors concluded that beta-blockers are effective in preventing bleeding and decreasing bleeding related mortality. In another meta-analysis by Pagliaro et al, that included 9 ran-

domised trials, there was a statistically significant reduction of bleeding risk (pooled odds ratio, 0.54 95% CI, 0.39 to 0.74), particularly in patients with medium or large size varices or in patients with varices and HVPG > 12 mm Hg. Nevertheless, although there was a tendency for mortality reduction, this did not reach statistical significance [3].

In a recent study by Abraczinskas et al [30], patients were randomized to receive propranolol that was later discontinued or placebo. Nine out of 49 patients (25 on propranolol, and 24 on placebo) developed variceal haemorrhage as a complication (6 on propranolol and 3 on placebo). This study showed that if propranolol is discontinued, the likelihood of bleeding is similar to that of patients not receiving propranolol. Moreover, patients who stop beta-blockers have increased mortality as compared to patients who receive no treatment. Thus, it appears that propranolol should be taken for life.

In conclusion, published studies on prophylactic use of propranolol in patients with large varices showed a significant reduction of bleeding risk, but without significant increase in overall survival [31].

ISOSORBIDE MONONITRATE (ISMN) VERSUS NO TREATMENT

Currently, beta-blockers are the first line treatment for the primary prevention of variceal bleeding [32]. However, they cannot be administered to a significant percentage of patients because of contraindications or side effects (15 - 25% of patients) [33].

Slow-release vasodilators like dinitrate isosorbide and ISMN could potentially constitute an alternative solution. The pharmacokinetics of ISMN makes it the first choice drug in this category. Several studies have been recently published using ISMN, as it appears to decrease HVPG by causing systemic vasodilation, hence reducing blood entering portal circulation. However, systemic vasodilation also causes GFR reduction and renal function deterioration [34].

In a multicenter randomized double – blind study that enrolled 133 cirrhotics with esophageal varices and contraindications or intolerance to beta-blockers (of which 67 received ISMN, and 66 received placebo), no difference was found in variceal haemorrhage risk among the two groups [33].

Therefore, it appears that available data are not sufficient to support monotherapy with ISMN in the primary prevention of variceal haemorrhage.

BETA-BLOCKERS VERSUS ISOSORBIDE MONONINTRATE (ISMN)

In 1993, Angelico et al. presented the results of a study that enrolled 118 patients and compared the efficacy of ISMN versus propranolol in the primary prevention of bleeding and suggested that ISMN is a safe and effective alternative to propranolol. Nevertheless, after 7 years of follow-up, the group of patients who received ISMN had higher mortality rate (only in patients over 50 years old) as compared to those who received propranolol [35].

In another study that enrolled 52 patients with ascites and esophageal varices, ISMN was less effective as compared to nadolol. ISMN was well tolerated but failed to prevent bleeding [36]. These studies emphasize the superiority of beta-blockers as compared to ISMN.

BETA-BLOCKERS AND ISOSORBIDE MONONITRATE (ISMN) VERSUS BETA-BLOCKERS MONOTHERAPY

The addition of ISMN on beta-blockers achieves greater reduction of portal pressure. In 1996, Merkel et al showed that the addition of mononitrate isosorbide to beta-blockers was more effective than monotherapy. After a mean follow-up of 30 months, the bleeding rate of patients who received nadolol was 18% as compared to 7.5% in the combination group [37]. Extended follow-up of these patients for more than 7 years confirmed the superiority of combination therapy over monotherapy with nadolol [38].

Nevertheless, other studies did not confirm these results. A study by the Spanish Variceal Haemorrhage study group enrolled 349 cirrhotic patients who were randomized to receive either propranolol and placebo (174 patients) or propranolol and isosorbide mononitrate (175 patients). This study showed that propranolol is very effective in the primary prevention of variceal haemorrhage, while the low residual risk was not further decreased when ISMN was added. Treatment side effects were significantly more frequent in the group that received combination therapy, because of the higher occurrence of headache [39].

In another study, 57 cirrhotics with large esophageal varices and red colour sings were randomized to receive either ISMN plus nadolol (30 patients), or nadolol plus placebo (27 patients). The study was interrupted due to increased mortality in a parallel study investigating the prevention of rebleeding in patients who received nadolol-containing and ISMN-containing treatment; consequently, it was not possible to draw valid conclusions [40].

It, therefore, appears that data are not sufficient to support the combination therapy with beta-blockers plus ISMN in the primary prevention of variceal bleeding since it is not clearly superior to monotherapy with beta-blockers.

BETA-BLOCKERS VERSUS SCLEROTHERAPY

Sclerotherapy has been compared to the administration of beta-blockers in primary prevention setting. In one study by Adreani et al in 1990, 126 patients were randomised in 3 groups: 43 patients received propranolol, 42 underwent sclerotherapy and 41 patients received placebo. After a two-years follow-up, 2 patients passed away in the propranolol group, 9 in the sclerotherapy group and 13 in the control group. 24 patients bled (2 in the propranolol group, 9 in the

sclerotherapy group and 13 in the placebo group). The risk of first variceal bleeding was significantly lower in patients receiving propranolol as compared to placebo ($p<0.004$) or endoscopic sclerotherapy ($p<0.03$) while no difference was found between sclerotherapy and placebo, confirming the superiority of propranolol [3].

BETA-BLOCKERS VERSUS SCLEROTHERAPY AND BETA-BLOCKERS

In the PROVA study (1991), among 286 patients enrolled in the study 73 patients underwent sclerotherapy, 68 patients received propranolol, 73 patients underwent both treatments and 72 patients received no treatment. Effects on bleeding were similar in all groups, but mortality was increased in the group that received combination treatment [3].

A recent study by Avgerinos, et al. assessed prospectively the effectiveness of combination treatment (sclerotherapy and propranolol) as compared to propranolol alone in cirrhotic patients with varices and high (>18 mmHg) intraesophageal variceal pressure. Forty-two patients received propranolol and 44 patients combination therapy. Median follow-up was 26.8±7.7 months and 24.6±9.8 respectively. 23% of patients who received combination treatment had at least one varices-related or portal gastropathy-related bleeding episode versus 14% in the group that received propranolol. Mortality was similar in both groups. Albumin was the only prognostic factor independently associated with survival. The authors concluded that endoscopic sclerotherapy should not be used for the primary prevention of variceal bleeding in cirrhotic patients [41].

So, it is well documented in the literature that sclerotherapy as a single agent or in combination with a beta-blocker should not be used in this setting.

BETA-BLOCKERS VERSUS LIGATION

Seven randomized studies [42-48] compared endoscopic treatment of high risk varices with beta-blockers.

In the De et al. study, 30 patients with 3 – 4 degree esophageal varices and HVPG ≥12 mmHG were randomized to receive propranolol (15 patients) or to undergo endoscopic ligation (15 patients). During follow-up (17.6±4.7 months), varices relapsed in 3 patients followed by bleeding in two of them. In the propranolol group, one patient bled from varices [42].

In a recent study, 172 patients with liver cirrhosis and II and III degree esophageal varices enrolled during a 6-year-period. 44 patients underwent ligation, 66 patients received propranolol and 62 patients received ISMN. Variceal haemorrhage was observed in 7% of patients. Bleeding risk was 6.2% (95% CI, 0.0%-15.0%) in the ligation group, 19.4% (95% CI, 0.1%-32.4%) in the group receiving propranolol, and 27.7% (95% CI, 14.2%-41.2%) in the group receiving ISMN. A substantial number of patients experienced side effects during treatment (45% in the propranolol group, 42% in the ISMN group, and 2% in the ligation group), necessitating discontinuation of treatment in 30% of patients who received propranolol and 21% of patients who received ISMN. There was no difference in mortality among the 3 groups. After a two year follow-up, there was a significant difference in bleeding risk between ligation and ISMN, favoring ligation, but not between ligation and propranolol [45]. The study has been criticised because only 9.1% of patients in band ligation group (4 patients) had large varices as compared to 18.2% of patients who received propranolol and 19.4% of patients who received ISMN, and this may be correlated with the favourable results of ligation. Lastly, 8% of patients had reduction of the heart rate without change of blood pressure, while it is well accepted that beta-blockers maximum effectiveness is achieved when heart rate and pressure drop by 25% [49].

Sarin et al. enrolled 89 patients in a prospective study, 44 of them received propranolol and 45 had band ligation. Median follow-up was 14±9, and 13±10 months, respectively. After 18 months, 12 patients in the propranolol group and 4 patients in the group that had band ligation bled. 3 out of 4 patients in the ligation group developed bleeding before the eradiation of varices while varices relapsed in 9 patients. 5 patients from each group died. Variceal haemorrhage was the cause of death for 4 patients in the propranolol group, and 3 patients in the band ligation group. There were no severe complications in the group of band ligation. In the propranolol group, treatment was discontinued in 2 patients because of side effects. The authors concluded that in patients with esophageal varices with high bleeding risk, endoscopic band ligation is safe and more effective than propranolol for the prevention of first bleeding [46]. However, serious concerns have been raised regarding the methodology of this trial and authors suggest that the available data are insufficient to support any change in our current practice [50].

In a meta-analysis, Imperiale et al. reported that endoscopic ligation decreased overall bleeding risk, but did not affect mortality; this led to the conclusion that it should be used only in patients with large esophageal varices who cannot tolerate beta-blockers. Five studies which compared ligation to no-treatment were analysed; two reported a statistically significant reduction of bleeding risk and bleeding-related mortality and one reported reduction of overall mortality. Four studies compared ligation to propranolol administration; only one favored ligation over propranolol in the reduction of risk for bleeding while none reported differences in mortality, either bleeding – related mortality or overall mortality [51]. Aoki et al. reported that ligation is an effective prophylactic treatment in many cases, but almost one quarter of patients can benefit more from receiving beta-blockers [52].

Recently, in a randomized multicenter study, 152 patients were randomized to receive either endoscopic treatment with ligation (75 patients) or pharmacological therapy with pro-

pranolol (77 patients). No differences were observed in terms of variceal bleeding or mortality [47].

The theoretical advantage of endoscopic ligation over beta-blockers is the absence of contraindications, except for the endoscopy, less problems with compliance and treatment efficacy in all patients. Nevertheless, a widespread program of prophylactic ligation would be very costly and it does require repeated endoscopies to treat and monitor reappearance of varices.

Two more trials have been published recently in this area [43,48). One [48] did not find any differences between banding and propranolol in the risk of first bleeding or mortality. The authors of the other study [43] suggested that propranolol-treated cirrhotics with high-risk oesophageal varices had a significantly higher rate of bleeding from oesophageal varices and greater cumulative mortality than those who had banding. It should be noted that in this study the selection criteria excluded patients are most at risk of first bleeding, (severe coagulopathy unresponsive to blood product transfusions, severe thrombocytopenia, gastric varices, documented hepatoma, portal or hepatic thrombosis and large-volume or tense ascites) i.e. the ones that clinicians may wish to treat intensively.

The conflicting results of the studies, the small number of patients enrolled, as well as EVL cost lead to the conclusion that beta-blockers remain, in our opinion, the first line treatment in the primary prevention of variceal haemorrhage.

LIGATION VERSUS SCLEROTHERAPY

The studies investigating the effectiveness of treatment with esophageal varices ligation versus sclerotherapy have reported conflicting results [53-55]. Gameel et al. supported ligation as the most effective method [53], Gotoh et al. favored sclerotherapy [54] and Svodoba et al. found that both treatments are equally effective [55]. These studies present significant heterogeneity and thus, the data cannot be evaluated meta-analytically. It should be noted that the likelihood of local complications following sclerotherapy is much higher and given the problems from the application of prophylactic sclerotherapy and the superiority of ligation versus sclerotherapy, these studies lack scientific and ethical basis, but they are quoted here for historical reasons.

LIGATION + BETA-BLOCKERS VERSUS LIGATION

In a recent study [56] 144 consecutive patients with high-risk varices were randomly allocated to EVL plus propranolol (Group I, n = 72) or EVL alone (Group II, n = 72). EVL was done at 2-wk interval until obliteration of varices. Eleven patients bled, 5 in Group I and 6 in Group II. All patients bled before the obliteration of varices and the actuarial probability of first bleeding after 20 months was 7% in Group I and 11% in Group II (p= 0.72). Six patients died in the combination and 8 in EVL group. The authors concluded that both, EVL plus propranolol and EVL alone are effective in the primary prophylaxis of bleeding from high-risk varices. The addition of propranolol does not decrease the probability of first bleeding or death in patients on EVL. However, the probability of recurrence of varices is lower if propranolol is added to EVL.

ANGIOTENSIN II RECEPTOR ANTAGONISTS

The antagonists of angiotensin II receptors decrease intrahepatic resistance but concerns have been raised for their administration in cirrhotic patients, because of their effects in systemic and renal circulation [57].

Losartan has been reported to be as effective as propranolol in reducing portal pressure in cirrhotics who do not take diuretics. It appears to be superior in the prevention of bleeding in cirrhotic patients without ascites, and in alcoholics [58]. Nevertheless, the results of two recent clinical studies [59,60] are not encouraging. Gonzales–Abraldes et al, investigated the hemodynamic and renal implications of losartan (25 patients) versus propranolol (15 patients) administered for 6 weeks in cirrhotic patients [59]. Losartan in a maximum dose of 50 mg/day decreased HVPG but also decreased mean arterial pressure and GFR in Child-Pugh B patients. Similar results were reported in the other randomized study where irbesartan was administered [60]. It appears that angiotensin II receptor antagonists should not be considered as an alternative treatment in patients with contraindications or intolerance to beta-blockers.

CONCLUSIONS

Endoscopic examination for the presence of esophageal varices and evaluation of their size should be performed in every patient diagnosed with liver cirrhosis. Surgery prevents bleeding, but the increased mortality and the increased risk of chronic encephalopathy makes this approach unacceptable. Prophylactic sclerotherapy should not be used, as it is relatively ineffective, inaccurate, and potentially risky. The treatment of choice is the administration of beta-blockers for life. It is an effective, cheap, easy to administer therapy, while it also prevents bleeding from portal gastropathy.

Primary prevention with band ligation appears to be safe and probably constitutes an alternative for a) patients with contraindications to beta-blockers, and b) patients that cannot tolerate the drug or do not have hemodynamic response to the drug administration. Nevertheless, it is an expensive treatment requiring specialized staff and it cannot prevent gastric mucosal bleeding. So far, data are insufficient to support the combination of beta-blocker plus ISMN or the combination

of endoscopic plus pharmacological therapy.

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When nature sculpts
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