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Primary prevention of portal hypertensive bleeding in cirrhosis

J. Vlachogiannakos, A. K. Burroughs

SUMMARY

Variceal bleeding due to portal hypertension represents the major complication that develops in patients with cirrhosis of the liver. The mortality of the first bleeding episode is still very high, so that primary prophylaxis to prevent bleeding from varices and portal hypertensive gastropathy is the current optimal therapeutic approach. The difficulty in identifying individual patients with varices who will bleed before they do so, can justify a strategy of prophylactic treatment for all patients with varices. We have evaluated the different therapies that have been assessed in randomized controlled trials for prevention of first bleeding, using meta-analysis where applicable. The current treatment of first choice is non-selective b-blockers; it is cheap, easy to administer, and is effective in preventing the first variceal hemorrhage and bleeding from gastric mucosa. Combination drug therapy of β-blockers and nitrates probably gives little added advantage. Injection sclerotherapy is contraindicated. The conflicting results of the randomized studies of endoscopic banding ligation (EBL), as well as the cost, do not warrant its use at present. However, EBL may be a reasonable alternative for patients who cannot tolerate, or have contraindications to β-blockers or no haemodynamic response to the drug therapy, but this must be proved in randomized trials.

Keywords: Cirrhosis, portal hypertension, varices, primary prophylaxis, β-blockers, endoscopic sclerotherapy, band ligation.

Liver Transplantation and Hepatobiliary Medicine, Royal Free Hospital, London, UK

Author for correspondence:

Dr Andrew K. Burroughs MB CHB Hons FRCP, Consultant Physician and Hepatologist, Liver Transplantation and Hepatobiliary Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK, Tel: 020 7472 6229, Fax: 020 7472 6226, e-mail: andrew.burroughs@talk21.com

INTRODUCTION

In cirrhotic patients prevention of first upper gastrointestinal bleeding from both varices and portal hypertensive gastropathy with non-selective beta-blockers is the current standard therapy. It reduces the bleeding complications associated with portal hypertension. However in several centres this is still not universal practice. This evidence is based on randomized controlled trials which recruited patients with large varices. New therapeutic regimens of combination drug therapy, beta-blockers and isosorbide, and endoscopic banding ligation have recently been evaluated. This review examines whether current clinical practice should be changed in the light of new data.

NATURAL HISTORY - PREDICTION OF THE RISK OF BLEEDING

Development of varices - Screening of patients

When cirrhosis is diagnosed, varices are present in about 60% of decompensated and 30% of compensated patients.[1] The threshold portal pressure gradient or its equivalent hepatic venous pressure gradient (HVPG) threshold for the development of varices is 10-12 mmHg, but not all patients with HVPG above this level have oesophageal varices.[2] There is little information on the incidence of development of new oesophageal varices. Two large studies[3,4] report a similar incidence of about 8% per year but 70% of patients are still free of varices after six years.[4] The presence and size of oesophageal varices has some correlation with the severity of liver disease and continued alcohol abuse. Continued abstinence from alcohol may result in decreasing size or even disappearance of varices. Abstainers have a significantly higher survival rate and a decreased probability of bleeding.[5]

Less data are available on the rate of enlargement of oesophageal varices. Pagliaro et al[4] reported that after

six years, 4% of the 225 patients without varices and 25% of the 118 patients with small varices developed large varices (occupying more than one third of oesophageal lumen). In contrast, during a mean follow-up of 16 months, in 84 patients, 19% without varices and 42% with small varices developed large varices (confluent varices that were not flattened by insufflation).[6] The different definition of "large" varices and the difference in the proportion of alcoholic and Child-Pugh class C patients (more in the French study),[6] may account for this discrepancy.

Given that beta-blockers are indicated for the prevention of first upper GI bleeding, and the fact that patients without varices do not bleed, the challenge is to identify those patients who have developed varices and are at risk of bleeding. Therefore, the assessment of the presence of gastroesophageal varices is important in the prognosis and management of patients with cirrhosis. Current recommendations state that all patients identified with cirrhosis of the liver should undergo diagnostic esophagogastroduodenoscopy (EGD) for the detection of oesophageal varices.[7] Two interobserver studies[8,9] showed that endoscopy is reliable in the evaluation of some variceal features and that the agreement between observers was good for the presence and size of varices, and the presence of red signs, which are the major endoscopic signs that predict risk of first bleeding. In a recent study, there was an excellent interobserver agreement (98.3%) for the presence or absence of varices, between several different pairs of experienced endoscopists from four different centers.[10]

As endoscopy is an invasive procedure and is unnecessary for well-compensated cirrhotics with little probability of having developed varices, a French group,[11] 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 of screening endoscopy. Recently, Schepis et al,[12] developed a non-invasive predictive tool to identify patients with oesophageal varices. They suggested that compensated cirrhotic patients should be screened by upper gastrointestinal endoscopy only when prothrombin activity less than 70%, platelet count less than 100 x 10^9/L, and ultrasonographic portal vein diameter greater than 13mm are observed, whereas those without any of these predictors should not undergo endoscopy. However, the investigators failed to confirm the results obtained in the first sample of 143 patients in a second cohort of 105 cirrhotic patients with similar demographic characteristics.[13] Thus, for the present, the risk of first variceal bleeding is best evaluated by EGD.

Nevertheless, there is no consensus on the optimal intervals for surveillance EGD. An upper gastrointestinal endoscopy every two years is considered sufficient for patients without varices.[4,6] A more strict surveillance with endoscopies at 1-year intervals is recommended in patients with small varices or alcoholics with advanced cirrhosis (Child-Pugh class C, continued alcohol abuse), such as those in the French study.[6] However, in a recent study,[14] published only in abstract form, it was considered that only patients with Child-Pugh class C alcoholic cirrhosis need annual endoscopic surveillance. Patients with well-compensated cirrhosis and no varices or only small varices should be endoscoped every three years and the remaining every two years.

Risk of first variceal bleeding

The incidence of variceal bleeding in 1228 patients who participated in 22 randomized controlled trials of either β-blockers or sclerotherapy compared to no therapy for prevention of first bleeding ranged from 15% to 68% (median 32%) with a median follow-up of 2 years.[4] Mortality of the first bleeding episode was high ranging between 30 and 50%.[15] About 60% of deaths were due to uncontrolled bleeding, either during the initial episode or due to early rebleeding. In a prospective study on the natural history of cirrhosis in 494 patients,[4] deaths from bleeding represented 38% of all deaths in patients with large varices, and 18% in the whole population.

Therefore the identification of patients with varices who will bleed before they do so is clearly important in order to offer effective prophylactic therapy to those who need it, and avoid it for those who do not, particularly if the therapy is invasive or costly. The risk factors for the first episode of variceal bleeding in cirrhotic patients include the severity of liver dysfunction (Child-Pugh classification), the size of varices (large greater than small) and the presence of endoscopic red color signs. The combination of these three factors is the basis of the NIEC (North Italian Endoscopic Club) index for the prediction of the first variceal bleeding.[16] However, the efficacy is far from optimal, as only a third of patients who present with variceal haemorrhage have the above risk factors.[12] Merkel et al,[18] enrolled 627 cirrhotic patients who were followed-up for two years or until first variceal bleeding and they reported recently a revised NIEC index, that includes the same predictive factors but gives a larger statistical weight to the size of varices and a decreased weight to Child-Pugh class. Validation of this

revised index in an independent sample of 84 patients showed good agreement between predicted and observed risk of bleeding. Moreover, new predictive factors have been sought that could be combined in the NIEC index (original or revised) in order to improve its validity.

The main interest has been to identify haemodynamic factors that could more readily reflect the pathophysiological changes, which lead to variceal bleeding. It is now well accepted that no bleeding occurs in the presence of varices if HVPG is below 10-12 mmHg.[19] Once this 12 mm Hg HVPG threshold is crossed, bleeding is expected to occur at some point.[20] However, the likelihood of bleeding is not related linearly to portal pressure when HVPG exceeds 12 mm Hg, although HVPG tends to be higher in those who bleed and in those with larger varices.[21]

Nevens et al, have shown prospectively, that variceal pressure is an independent predictive factor for the first variceal bleeding in patients with cirrhosis as well as with non cirrhotic portal hypertension.[22,23] It has also been suggested in a cross-sectional study that variceal rupture is more closely associated with an increased variceal pressure than with increased HVPG.[24] The NIEC index combined with intravariceal pressure could be a more precise predictor of the first bleeding episode.[25] but there are problems with the technique of measuring pressure in oesophageal varices. All these studies[22-24] used a pressure-sensitive gauge attached to the distal end of the endoscope. Although it does not require puncture of the varices, it is cumbersome and needs specialized equipment and training. In addition the size of the varices has a significant influence on the measured pressures in the capsule and on the precision of those measurements.[26]

Other possible independent risk factors include the presence of gastric varices,[27] the patency of the portal and hepatic veins and the velocity and direction of portal flow (as determined with a Doppler ultrasonographic probe).[28] Doppler ultrasonography (US) provides a non-invasive access to the portal system and allows for the estimation of both arterial and venous flow as well as repeated measurements of various haemodynamic parameters.[29] Although diagnostic ultrasound is widely used in the evaluation of portal hypertension in cirrhotic patients, Doppler is rarely employed, and its actual utility is still debated. Alcohol abuse obviously plays a role in the occurrence of the first bleeding episode, as may be inferred from virtually every study.[31]

Recently, Goulis et al[32] proposed that endotoxaemia in patients with cirrhosis may be the critical factor that triggers bleeding. In patients with large varices and high wall tension, the release of endotoxin into systemic circulation during episodes of bacterial infection results in further increase in portal pressure through the induction of endothelin and possibly vasoconstrictive cyclooxygenase products. The subsequent contraction of hepatic stellate cells causes a rise in intrahepatic vascular resistance. Furthermore, endotoxin-induced nitric oxide and prostacyclin, and prostacyclin induced by endothelin could inhibit platelet aggregation, which may result in further deterioration of primary haemostasis at the level of the varix. The combination of these two factors could lead to the start of variceal bleeding. There is good experimental data to make this hypothesis plausible, but, as yet, no clinical data to substantiate this.

The difficulty in obtaining more reliable information for the risk of first bleeding in an individual patient, and in particular the fact that a third of patients who bleed, have no worst risk factors for bleeding,[17] can justifiably lead to a strategy of treating all patients with varices prophylactically, providing the treatment were to be safe, inexpensive and easy to use, which is the case with non-selective β-blockade. However, as described below, most randomized studies have included only patients with large varices and/or red signs, which form the minority of patients.

RANDOMIZED CONTROLLED TRIALS FOR PREVENTION OF FIRST VARICEAL BLEEDING

The randomised controlled trials, have been evaluated using meta-analysis where applicable. The main end points selected were the following: (a) first bleeding episode; (b) mortality and (c) incidence of complications. Pooled odds ratios (POR) represent the pooled estimates of efficacy, obtained by Mantel-Henszel method (fixed effect model) as modified by Robbins,[33] with 95% CI. Statistical evaluation of heterogeneity by x^2 test was used to evaluate whether the variation in treatment effect within trials of the same group was greater than might be expected; heterogeneity was considered to be present if $p<0.05$. If statistical heterogeneity was found the calculation of pooled OR was performed by the Der Simonian and Laird method,[34] which is recommended for meta-analysis of studies with significant heterogeneity.

Surgery compared with non-active treatment

Four prophylactic shunt trials,[35-38] which were the first randomised-controlled trials in portal hypertension, included 302 patients. Variceal bleeding was significantly

reduced (OR, 0.31 [95%CI, 0.17-0.56]) in the treated group but survival was significantly worse (OR, 1.6 [95%CI, 1.02-2.57]) compared to no treatment. Moreover, the risk of chronic or recurrent encephalopathy was signicantly increased (OR, 2.0 [95%CI, 1.2-3.1]) in shunted patients. In view of the mortality data and the serious side effects, prophylactic shunt surgery has been abandoned world-wide. The advent of liver transplantation removes any rationale for prophylactic surgery of any kind in cirrhotic patients.

Inokuchi et al from Japan who compared devascularization procedures or selective shunts versus nonactive treatment,[39] showing a significant reduction in bleeding risk (7% at 5 years versus 42% in the non-operated group) and mortality (22% vs 49% for medical patients). However, a variety of procedures were performed in the 22 participating institutions in the 60 patients allocated to surgery. In addition, patients in the medical group received neither sclerotherapy nor pharmacologic agents for the control of acute variceal bleeding. Thus, the results of this study are not clinically relevant today.

Sclerotherapy compared with non-active treatment

The success of endoscopic sclerotherapy in the treatment of acute variceal bleeding led to extensive evaluation for the prevention of the first variceal bleed. There are 20 trials,[40-59] of which 4 are published in abstract form[55-58] including a total of 1756 patients. The principal feature of these trials is the statistically significant heterogeneity ($p<0.001$) in the direction and size of the treatment effect for bleeding and death, so that meta-analysis is not possible. The first trials reported promising results following sclerotherapy with less bleeding, and in some a reduced mortality.[41,47,48] However they were of poor quality[60] and also had unexpectedly high rates of bleeding in the control groups. Furthermore, control group patients did not receive emergency sclerotherapy for the treatment of acute variceal bleeding. Subsequent larger trials did not confirm benefit and indeed some trials have suggested that prophylactic sclerotherapy is deleterious. Two of the larger studies had to be stopped because there was a significant survival advantage for patients randomized to the control group.[52,54] In evaluating endoscopic sclerotherapy it must be remembered that it is an expensive and invasive treatment, which is associated with potentially serious complications. It is possible that the harmful effect of sclerotherapy in patients at a low risk of first bleeding is due to side-effects and complications outweighing the potential advantage. In contrast, Paquet et al,[59] reported that sclerotherapy reduced the incidence of first variceal hemorrhage and prolonged survival in high risk patients selected with varices grade III or IV, with red spots, and HVPG >16mmHg. However these selection criteria have not been reproduced by others, and therefore sclerotherapy cannot recommended[61] as routine prophylactic treatment. Lastly Strauss et al,[62] have published a long term follow-up of their initial study[57] on prophylactic sclerotherapy of small oesophageal varices in cirrhotic patients. After a mean time of 60 months (range 36-89 months) patients allocated to sclerotherapy had a higher prevalence of bleeding (36.8%) as compared with controls (9.5%, $p=0.044$), although mortality was similar in both groups. It is important to have this background when considering prophylactic banding.

β-blockers compared with non-active treatment

The optimal prophylactic regimen should be easy to administer, have relatively few side effects, and be reasonably effective. Drug therapy potentially fulfils these criteria best. In addition, drug therapy protects against bleeding from portal hypertensive gastropathy, which accounts for a sizeable proportion of first bleeding episodes.[63] Non-selective β-blockers (propranolol, nadolol) are first line therapy. They decrease the splanchnic blood flow by reduction of cardiac output and reflex splanchnic arterial constriction.[64] In addition, they have a direct effect on portocollateral resistance, decreasing azygos and gastroesophageal collateral blood flow.[65] Nevertheless, there is a wide individual variation in the reduction of portal pressure achieved with β-blockers, which is not related to the dose of the drug, aetiology or severity of portal hypertension, or circulating levels of adrenaline and noradrenaline.[66]

There are 9 prophylactic trials using b-receptor blockade comprising 996 cirrhotic patients, selected on the basis of having large varices;[50,54,57,67-72] 7 trials used propranolol[50,54,57,67,70-72] and 2 used nadolol.[68,69] Seven trials were published as peer-reviewed articles[50,54,67-71] and 2 in abstract form.[57,72] One of the latter trials[72] was an outlier reporting a very low bleeding rate in non-treated patients. This study caused statistically significant heterogeneity in the evaluation of first bleeding in a comprehensive analysis evaluating the effect of b-blockade therapy in the prevention of variceal bleeding. The heterogeneity was disappeared when the trial[72] was withdrawn from the analysis. There was a statistically significant bleeding risk reduction with b-blockers[73] either including (OR, 0.54 [95%CI, 0.39-0.74]) or excluding (OR, 0.48 [95%CI, 0.35-0.66]) the outlier trial.[72] The average number of patients that were needed to treat to prevent one bleeding epi-

sode was 11 [95% CI, 8-11]. There was no heterogeneity in the evaluation of mortality (p= 0.19), which was reduced with b-blockers but this did not achieve statistical significance (OR, 0.75 [95%CI, 0.57-1.06]).

B-blockers have been shown to be effective independently of cause and severity of cirrhosis, presence of ascites and variceal size in an analysis of individual patient data from 4 of the above trials.[74] Current recommendations are that patients with large varices who have not bled should be offered prophylactic β-blocker therapy.[7] There are insufficient data to make recommendations for small varices but numerically those with small varices may be as many as those with worse risk factors for bleeding. As mentioned above, propranolol could be used universally as it is cheap (£10/year for 80mg bd in the UK), safe and easy to administer. Bleeding may occur after stopping b-blocker therapy, suggesting that therapy should be maintained life-long.[75] Currently the maximum tolerated dose should be given to the patient, usually an average of 120mg/day, but there is individual variation. As propranolol has also been shown to prevent both acute and chronic bleeding from portal hypertensive gastropathy in a single blind randomised study,[63] it prevents bleeding from both varices and PHG. A recent cost-effectiveness analysis in the USA supports the use of propranolol as the most cost-effective therapy for prophylaxis against initial variceal bleeding in all risk groups of cirrhotic patients with oesophageal varices.[76]

However, there are problems with contraindications and intolerance to β-blockers. Severe and moderate congestive heart failure, severe chronic obstructive lung disease, peripheral vascular disease and insulin-dependent diabetes mellitus are relative contraindications to their use. Moreover 3 to 27% of patients develop side effects and half of them require withdrawal of therapy.[77] Although these are usually reversible after discontinuation of the drug, and importantly no fatal complications have been reported in cirrhotic patients, compliance is reduced and a sizeable proportion of patients at risk of first bleeding are not protected.

In addition, approximately one-third of patients do not exhibit any decrease in portal pressure despite adequate β-blockade (2), although this proportion may be less in patients who have never bled. The technique of wedged hepatic vein pressure (HVPG) measurement, a straightforward venous cannulation technique in the groin, allows one to target the drug therapy for the individual patient, and assess efficacy.[19] Adequate protection from the risk of bleeding may be achieved when the HVPG is decreased below 12mmHg[78] or at least by 20% from baseline.[79] Merkel et al,[80] assessed the role of the haemodynamic response to nadolol or to nadolol plus nitrates in predicting clinical efficacy of prophylaxis in 49 cirrhotic patients. They measured the HVPG before and one to three months after starting therapy and they found that the probability of bleeding at three years of follow-up was significantly higher in poor responders (41%) than in good responders (7%; p=0.0008). Alternatively, De et al,[81] have recently proposed that single-sitting haemodynamic assessment of acute response to high dose (80mg) oral propranolol (HVPG measured before and 90 min after propranolol) clearly differentiates between responders (defined as having achieved a >20% reduction in HVPG) and non-responders. However, although HVPG is easy to measure,[19] it is costly, involves hospital stay and would not be feasible when considering a universal use of β-blockade for all patients with varices. Thus empirical titration of propranolol dose (as in the original trials) is still current practice.

At present there is currently no adequate data to recommend alternative medication other than non-selective b-blockers for primary prophylaxis of variceal bleeding.[7] The addition of isosorbide-5-mononitrate (ISMN) to β-blockade has been evaluated in two studies.[82,83] In the first,[82] the combination with nadolol was more effective in reducing bleeding, with only a small increase in side effects. Recently, the same group reported the long-term results over 7 years in 146 cirrhotics with varices.[84] Sixteen in the nadolol group and eight in the combination therapy group bled (p=0.32). The cumulative bleeding risk was 29% and 12% respectively (17% difference with 95% CI for the difference 1-23%). Addition of isosorbide-5-mononitrate did not increase the incidence of liver failure, development of ascites or renal insufficiency; however, five patients requested discontinuation of nitrates due to side effects. In the second study,[83] 349 cirrhotic patients were randomized to receive a combination of propranolol and ISMN or propranolol and placebo. The 1 and 2 year actuarial probability of variceal bleeding was similar for both groups (7.5% and 10% for propranolol + placebo vs. 7.6% and 12.7% for propranolol + ISMN; NS) with no difference in mortality or in the number of patients developing ascites or renal failure. Adverse effects were significantly more frequent in the propranolol + ISMN group and the authors concluded that nitrates do not provide any further benefit when given in combination with propranolol.

Moreover, in a study of direct comparison between propranolol and isosorbide-5-mononitrate for the prevention of variceal bleeding, nitrates were associated with

a higher long-term mortality in elderly patients.[85] So, current data suggest that sole use of nitrates may be dangerous and they should only be used as an additional therapy to β-blockers.

The efficacy of isosorbide-5-mononitrate (ISMN) as compared with placebo in the prevention of the first variceal bleeding in patients with contraindications or intolerance to β-blockers was evaluated in a recent study published only in abstract form.[86] The 1 and 2 year actuarial probability of bleeding was significantly greater in the ISMN group (17% and 29% vs 7% and 14% in the placebo group; $p<0.05$) with no significant differences in the probability of survival (ISMN 85% and 67%; PLA 88% and 80%, NS). The above results further argue against the use of nitrates as monotherapy in the primary prophylaxis of variceal bleeding.

Recently, Avgerinos et al,[87] evaluated the efficacy of the combination of propranolol and endoscopic sclerotherapy versus propranolol alone in cirrhotic patients with varices and high (>18 mmHg) intraoesophageal variceal pressure. After a mean follow-up of 25 months, combination therapy was not better than propranolol, with respect to the incidence of bleeding or mortality. Furthermore, 52% of patients in the combination group developed complications as compared to 19% of patients in the propranolol group ($p=0.002$). The results of this trial indicate that the addition of endoscopic sclerotherapy does not increase the effectiveness of β-blockers and reinforces the fact that it may be harmful in patients with varices who have never bled.

Variceal ligation compared with non-active treatment

In recent years, endoscopic variceal ligation (EVL) has replaced endoscopic sclerotherapy (EIS) as the method of choice for the prevention of rebleeding. In comparative trials and in a meta-analysis of studies including 547 patients,[88] ligation was more effective than sclerotherapy in preventing rebleeding, in part because it resulted in faster eradication of varices and had fewer complications. However, it is still not known whether EVL is of benefit to patients with esophageal varices which have never bled. Given the published literature and the consensus on the use of non-selective β-blockers[7] one would have expected that banding ligation would be compared to β-blockade. However, surprisingly, 6 trials, have been performed against no therapy. The authors believe these were unethical trials but they are commented on here as a background to the β-blocker versus banding studies.

The six studies of prophylactic variceal ligation included 612 patients only with high-risk oesophageal varices,[89-94] two only in abstract form[93,94] (Table 1). Variceal ligation significantly reduced the risk of first variceal bleeding (POR, 4.26 [95%CI, 2.85-6.37]) and, surprisingly, mortality (POR, 2.44 [95%CI, 1.7-3.51]). No serious complications resulted from variceal ligation. Superficial ulcerations were noted in the majority of patients one week after the first session of ligation. Retrosternal pain, dysphagia and fever were reported in approximately one third of patients but they were transient and lasted for a few hours to 1 or 2 days. Nevertheless, two patients died; one because of oesophageal perforation related to the insertion of the overtube,[89] and one after post-EVL ulcer bleeding complicated with aspiration pneumonia.[91]

Variceal ligation compared with β-blockers

Recently, four randomized trials reported the comparison of endoscopic band ligation of high-risk esophageal varices compared to propranolol[95-98] (Table 2). In the first, from Sarin et al,[95] comprising 89 patients, there was a significant reduction in bleeding from 43% in the

Table 1. Randomised controlled trials of endoscopic band ligation compared to nonactive treatment for the prevention of first variceal bleeding

Study (ref)	No of patients C/T	Child C (%)	Bleeding C/T	Death C/T
Sarin (89)	33 / 35	31%	13 / 3	8 / 4
Lay (90)	64 / 62	38%	38 / 12	37 / 17
Lo (91)	63 / 64	28%	14 / 8	23 / 16
Svoboda (92)	50 / 52	12%	27 / 15	19 / 12
Chen ¶ (93)	76 / 80	NR	28 / 7	31 / 15
Gameel ¶ (94)	17 / 16	NR	3 / 0	0 / 1
POR (95% CI)			4.26 (2.85-6.37)	2.44 (1.7-3.51)

C, control; T, Band ligation; NR, not reported; ¶ abstract only; POR, pooled odds ratio

propranolol group to 15% in those treated endoscopically. The rate of bleeding in the propranolol group was higher-than-expected. Potential explanations are the lower mean dose of propranolol that was administered (70mg per day) compared to that in previous studies (123mg per day). Most importantly, the rate of bleeding in the propranolol group was the same as that in the non-treated group in a previous trial by the same authors in which the same selection criteria were used. [89] In addition, despite a significant reduction in bleeding in the ligation group, there was no significant difference between the two treatment groups either in overall mortality or in mortality due to bleeding.[99] Moreover, a number of methodological considerations raised concerning the Sarin's study have also been raised in a recent published commentary.[100] In contrast with other regions of the world, 9% of their patients had non-cirrhotic portal hypertension. When these patients were excluded from the analysis the differences did not reach statistical significance. Despite the intention to treat strategy, one patient assigned to the ligation group who failed to show up the next day after randomization was not included in the analysis. As the results reached only borderline statistical significance the outcome of this patient may have affected the conclusions. Finally, the authors did not provide information on the causes of bleeding in the propranolol group. It is assumed that all these patients bled from varices. It is obvious that any other cause of bleeding would eliminate any difference between the two groups. In the second study, from De et al,[96] only 30 patients were included and there was no difference in bleeding between the two groups. The results of the third study,[97] published in abstract form, suggested that ligation has no advantage over propranolol. In the fourth study,[98] also in abstract form, 61 patients were allocated either to endoscopic band ligation (31 patients) or to propranolol (30 patients). Ligation was slightly better than propranolol in the prevention of bleeding and in the mortality rate, but the difference was not statistically significant. Meta-analysis of the four above studies, including 290 patients, showed bleeding was significantly reduced but this was a border-line effect (POR 1.97 [95%CI 0.99 - 3.88]) and mortality was unchanged (POR 1.26 [95% CI 0.67 - 2.35]).

The theoretical advantages of EVL therapy over β-blockers are that there are no contraindications except for the endoscopic procedure, fewer problems with compliance (providing the patient attends for endoscopic sessions), and the therapy is effective overall (providing varices are eradicated). However, a widespread programme of prophylactic ligation would be very costly and it does require repeated endoscopies to treat and monitor reappearance of varices.

The conflicting results of the randomized studies and the small number of patients and events, as well as the cost of EVL, do not warrant any change in the current practice of giving propranolol as the treatment of first choice for the primary prevention of variceal bleeding.

Variceal ligation compared with sclerotherapy

The efficacy of endoscopic ligation (EVL) in comparison with endoscopic sclerotherapy (EIS) for the primary prevention of variceal bleeding was evaluated in three small studies,[92,94,101] of which one was only presented in abstract form[94] (Table 3). The results were conflicting. One study suggested that EVL is less effective than EIS.[101] The second study concluded that both are similarly effective[92] and the last one favored the prophylactic use of EVL instead of EIS.[94] Thus it is not surprising that there is significant statistical heterogeneity in the meta-analysis (p=0.045) for bleeding, and thus the data cannot be evaluated meta-analytically. There is no significant difference for mortality (POR 0.84 [95%CI 0.35 - 2.05]). However, it is surprising that the authors compared banding ligation with endoscopic sclerotherapy and

Table 2. Randomised controlled trials of endoscopic band ligation compared to propranolol for the prevention of first variceal bleeding

Study (ref)	No of patients EBL / PRO	Child C (%)	Bleeding EBL / PRO	Death EBL / PRO
Sarin (95)	45 / 44	31%	4 / 12	5 / 5
De (96)	15 / 15	13%	2 / 1	NR
Lui ¶ (97)	44 / 66	NR	3 / 9	11 / 18
Song ¶ (98)	31 / 30	NR	6 / 7	5 / 8
POR (95% CI)			1.97 (0.99-3.88)	1.26 (0.67-2.35)

EBL, band ligation; PRO, Propranolol; NR, not reported; ¶ abstract only; POR, pooled odds ratio

Table 3: Randomised controlled trials of endoscopic band ligation compared to endoscopic sclerotherapy for the prevention of first variceal bleeding

Study (ref)	No of patients	Child C (%)	Bleeding	Death
EBL / EIS		EBL / EIS	EBL / EIS	
Gotoh (99)	25 / 25	18%	5 / 0	NR
Svoboda (92)	52 / 55	12%	15 / 11	12 / 11
Gameel ¶ (94)	16 / 17	NR	0 / 2	1 / 1
POR (95% CI)			*	0.84 (0.35-2.05)

EBL, band ligation; EIS, End. Sclerotherapy; NR, not reported; ¶ abstract only; POR, pooled odds ratio

* Statistical heterogeneity in a meta-analysis (p=0.045)

not β-blockers, but these studies give extra information on the efficacy of banding.

Considering all 11 randomized trials in which prophylactic banding was used, bleeding occurred in 13.8% (range 0-29%) of 470 patients, after a median follow-up of 17.8 months (range 12-36 months). Variceal recurrence was noted in 30% (range 18.7-56%) of patients after initial eradication, emphasizing the need for endoscopic monitoring and retreating these patients, and the cost of such therapy.

PREVENTION OF THE DEVELOPMENT OF VARICES

Experimental models of portal hypertension have shown that early treatment with propranolol ameliorates the development of collaterals, suggesting a possible clinical use of β-blockers in the prevention of development of varices.[102,103] A randomized, double-blind trial was conducted by Cales et al[104] to evaluate propranolol in the prevention of the development of large oesophageal varices in patients without varices or with small varices. One group of 102 patients received propranolol (160mg per day) and a second group of 104 patients received a placebo. At two years, the proportion of patients with large varices was 31% in the propranolol group and 14% in the placebo group. The authors suggested that propranolol administration could not be recommended for the prevention of large oesophageal varices in patients with cirrhosis. However, the results of the study are difficult to interpret because 41% of the patients in the propranolol group and 31% in the placebo group were lost in follow-up. Furthermore, it is not clear how many patients without varices and how many with small varices developed large varices after two years. Another study was performed in unselected patients with mild or moderate chronic liver disease from different causes, but not all with cirrhosis, receiving either propranolol or placebo.[105] The results did not show any significant difference between the two groups in the occurrence of variceal bleeding or survival rate. However, the rate of bleeding in the placebo group was very low (3.8%), probably because many of the patients included were not cirrhotics. Moreover, data on the presence of varices were not available in 30% of patients.

Recently, the effect of timolol, a non selective β-blocker, was evaluated with respect to the portal pressure in compensated cirrhotic patients without varices, and the response was compared with that of patients with varices.[106] Timolol was more effective in reducing portal pressure in cirrhotic patients without varices than in patients with varices, suggesting that non-selective β-blockers are more effective in the treatment of portal hypertension when administered at early stages, before the development of varices. The results are promising and this is being tested in a randomized double - blind controlled trial in a four-centre study (New Haven, Boston, Barcelona, London) sponsored by the National Institutes of Health.

CONCLUSIONS

The data from prophylactic trials indicate that screening for varices in cirrhotics should be part of routine clinical practice. If these are found, prophylactic treatment to prevent first variceal bleeding should be given. The current treatment of choice is non-selective β-blockers and in the authors' opinion, all patients with varices should be offered this therapy. Variceal ligation may be a reasonable alternative for patients who cannot tolerate, or have contraindications to β-blockers or no haemodynamic response to the drug therapy, but this must be proved in randomized trials. However banding is unlikely to become a routine prophylactic treatment as it is much more expensive and less applicable than β-blockers and also will not prevent gastric mucosal bleeding.

The future is to improve on current medical therapy and to validate easily measured surrogate markers of portal pressure response.

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