Primary Prophylaxis of Bleeding from Esophageal Varices in Cirrhosis

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Prophylaxis of the first bleeding from esophageal varices became a clinical option more than 20 years ago, and gained a large diffusion in the following years. It is based on the use of nonselective beta-blockers, which decreases portal pressure, or on the eradication of esophageal varices by endoscopic band ligation of varices. In patients with medium or large varices either of these treatments is indicated. In patients with small varices only medical treatment is feasible, and in patients with medium and large varices with contraindication or side-effects due to beta-blockers, only endoscopic band ligation may be used. In this review the rationale and the results of the prophylaxis of bleeding from esophageal varices are discussed. (J CLIN EXP HEPATOL 2013;3:198–203)

In historical terms, prophylaxis of the first variceal bleeding came last within the context of varices management, over the last decade on the past century. This was after the treatment of acute variceal bleeding, which was initially defined in the '50s, and the prevention of recurrent variceal bleeding, which started to be effectively treated in the '70s. Being the last management step, researchers and doctors were able to take advantage of the pathophysiological investigations which were previously performed in portal hypertension, and of the experience accumulated for purposes of slightly different but still related clinical indications.

It was suggested⁴ that the presence of a patent para-umbilical vein, being a collateral circulation that does not feed the esophageal varices, may bear a protective role on variceal occurrence and rupture. The observation⁵ that in a prospective study the rate of formation of esophageal varices in patients without varices at the beginning of follow-up was not influenced by the presence or absence of a patent para-umbilical vein contrast with this hypothesis, and is consistent with the concept that abdominal collaterals are a hint of a more advanced step in the natural history of the disease, and they tend to progress in agreement.

NATURAL HISTORY OF GROWTH OF ESOPHAGEAL VARICES

The median time from the occurrence of cirrhosis to the development of esophageal varices is difficult to determine, due to the uncertainty in the time of onset of cirrhosis. However, in patients with established cirrhosis without varices, a roughly linear course of occurrence of varices was observed, with an incidence around 9% per year.¹ A higher Child-Pugh score was not a risk factor for the occurrence of varices,² confirming the linearity of the course, but the observation of worsening liver function³ or low platelet count and prolongation of prothrombin time were predictors of occurrence of varices. After the occurrence of varices, an aggravation was more frequent in patients with alcoholic etiology or with more advanced liver disease.¹

PATIENTS WITHOUT OESOPHAGEAL VARICES (PRE-PRIMARY PREVENTION)

The prevention of the formation of oesophageal varices would be clinically relevant, since it would abolish the risk of variceal bleeding from the beginning, by treating patients who have not yet developed this complication. A strategy for prevention would also be reasonable, since the formation of varices is a very frequent event in the course of the disease.

Because of the difficulties in performing long-term intervention studies in patients without a clinically relevant condition, to date, only one trial has been performed on the prevention of varices formation.⁶ This was a multi-centre double-blind study in 213 patients with documented cirrhosis, portal hypertension defined as HVP ≥ 6 mmHg, without oesophageal or gastric varices on endoscopy, aimed at comparing the occurrence of varices in patients treated with a nonselective beta-blocker (timolol) versus placebo. Patients randomized to timolol showed a significant decrease in HVP, but the percentage of patients who did not reach the primary end-point (formation of varices or variceal bleeding) was nearly identical in the two groups.

Keywords: beta-blockers, band ligation, portal hypertension

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Abbreviation: RWM: red wale marks

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This disappointing conclusion was interpreted as suggesting that in these patients, the pathophysiological mechanisms leading to portal hypertension (hyperdynamic circulation and increase in portal inflow) were weakly operating, and that non-selective beta-blockers might have been ineffective because of the lack of the target on which they are meant to operate. An alternative explanation is that the effect might have been too small to be demonstrated, in relation to the study size and the length of follow-up. Indeed, during the study, nearly half of the patients were withdrawn from treatment or decreased the dose, and 20% were non compliant. No further trial has assessed this issue, and it is unlikely that this might be done in the near future. According to the available evidence, all clinical practice guidelines^{7,8} agree that beta-blockers cannot be recommended to prevent the formation of oesophageal varices.

RISK OF BLEEDING IN RELATION TO THE CHARACTERISTICS OF ESOPHAGEAL VARICES

After the formation of varices, their risk of bleeding is variable, and is related to several factors, including the size and the features of the varices, and the severity of the underlying liver dysfunction. According to the ‘explosive theory’ of variceal rupture,⁹ varices rupture because the wall tension overwhelms the resistance of the variceal tissue, and the wall tension progressively increases in relation to the increase in variceal size and transmural pressure, and the decrease in wall thickness. In agreement with such theory, the most utilized and documented predictive index of first variceal bleeding, the NIEC index,¹⁰ which was proposed within the context of a multicentre study and then validated in several different settings, contains a semi-quantitative classification of variceal size, the presence of red wale marks (i.e. the expression of a very thin wall), and the Child-Pugh class, which is considered a surrogate marker of portal pressure (i.e. the transmural pressure within a varix, which cannot be easily measured in the general population).

According to this index (Table 1), one year risk of bleeding may vary from 6 to 76%, according to the charac-

teristics of the varices and of the patient. Different predictive indexes,¹¹ or modifications of the NIEC index,¹² albeit more precise in their predictive ability, have not gain the popularity of the original index.

In consideration of the large spectrum of bleeding risk in patients with varices, it is apparent that any clear-cut separation between small (or low-risk) varices, and large (or high-risk) varices is arbitrary, and should be based on reasonably simple criteria. Generally, varices are considered small if the largest varix is small than 5 mm (i.e. the opening size of an endoscopic biopsy forceps), or F1 according to the Japanese classification (linear varices occupying less than 1/3 of the oesophageal radius), or varices occupying less than 25% of the oesophageal lumen according to the ILCP classification.

Usually, patients with small varices have an HVPG lower than that of patients with large varices, and the difference has been reported to be significant only in some series.^{13,14} Overall risk of a first variceal bleeding in untreated patients is around half that of patients with large varices but it is not negligible (approximately 10% at two years).^{10,11,15,16} Non-selective beta-blockers decrease portal pressure in patients with small varices to the same extent as they do in patients with large varices.¹⁷ Thus, patients with small varices are quantitatively rather than qualitatively different from patients with large varices, and represent an earlier stage of the same pathophysiological condition.

PROPHYLAXIS OF VARICEAL BLEEDING IN PATIENTS WITH SMALL VARICES

Treating patients with small varices may be useful if the increase in size of the varices, which is associated with an increased risk of bleeding, can be delayed. This way, a decrease in bleeding risk should ensue. In addition, treating patients from the stage of small varices may have the additional benefit of abolishing the need for endoscopic surveillance of small varices, which is required to recognize a worsening of the varices, and the consequent change in treatment strategy. Since surveillance strategies generally imply an annual follow-up examination, and compliance to surveillance is often sub-optimal, starting treatment from small varices may be helpful in decreasing the risk

Table 1 Estimated risk of a first variceal bleeding according to the parameters included in the NIEC index (Ref. 10). RWM = red wale marks.

	Child-Pugh A			Child-Pugh B			Child-Pugh C		
	Small	Medium	Large	Small	Medium	Large	Small	Medium	Large
RWM 0	6	10	15	10	16	26	20	30	42
RWM 1+	8	12	19	15	23	33	28	38	54
RWM 2+	12	16	24	20	30	42	36	48	64
RWM 3+	16	23	34	28	40	52	44	60	76

of bleeding over the period of time between worsening of the varices and endoscopic proof of such worsening.

For these reasons, a few years ago we performed a randomized controlled trial aiming at assessing whether treatment with the beta-blocker nadolol in patients with cirrhosis and small esophageal varices delays variceal growth into large oesophageal varices and decreases the risk of bleeding.¹⁷ Eighty-three patients were randomized to nadolol and 78 to placebo; patients were followed for up to 60 months (Figure 1). Patients randomized to nadolol showed a decreased risk of variceal growth, a decreased risk of variceal bleeding but no significant decrease in mortality. It was concluded that in patients with small esophageal varices it is reasonable to start prophylaxis with non-selective beta-blockers. The lack of an effect on mortality was attributed to the sample size of the study, as very few patients in either arm died of variceal bleeding. No further trial has been performed to date. The only comparative data can be obtained by subgroup analyses of patients with small varices included in two trials of patients with large and small varices (mostly with large varices) treated with propranolol or placebo.^{18,19} A meta-analysis of such data is reported in Figure 2. In consideration of the limited amount of available data, practice guidelines are cautious, and suggests that such patients may (or should) be treated with beta-blockers although further studies are required to confirm their benefit.

PROPHYLAXIS OF VARICEAL BLEEDING IN PATIENTS WITH MEDIUM OR LARGE VARICES

Based on RCT and meta-analyses dating back over 20 years ago, it was clearly established that beta-blockers are effective in preventing the first variceal bleeding and decreasing the risk of death from bleeding.²⁰ Over the same years, several trials assessed the use of endoscopic sclerotherapy within the same setting, with conflicting results; the observation of a relevant 'quality effect' (i.e. the beneficial effect

Figure 1 Course of the risk of growth of esophageal varices in patients treated with nadolol or placebo (from Ref. 17).

Figure 2 Meta-analysis of beta-blockers versus placebo in the prophylaxis of first variceal bleeding in patients with small esophageal varices.

was limited to trials of low quality) eventually led to the abandonment of this procedure in the prophylaxis setting.²¹

In the subsequent years, the endoscopic armamentarium was improved with the development of endoscopic band ligation, and it soon became apparent that this procedure was safer, more effective, and less prone to individual variations. A few trials showed that it was more effective than no treatment.^{22,23} A series of meta-analyses (Table 2) of the numerous trials comparing it to non-selective beta-blockers showed a better effect of endoscopic treatment,²⁴⁻²⁷ no difference in survival, and a tendency to a quality effect. Side-effects were more frequent but less severe with medical treatment. A series of potential bias sources were highlighted: i) the only trial showing significant improvement in outcome with band ligation had a very high rate of bleeding with beta-blockers but a very low dose of propranolol was given, suggesting sub-optimal medical treatment²⁸; ii) a trial was interrupted at the time of the largest difference in bleeding in order to maximize the differences in outcome²⁹; iii) in some trials follow-up was too short for a fair comparison between treatments^{28,30}; iv) in one trial, only preliminary results were provided, and no full report was available several years from initial publication.³⁰

Table 2 A series of recent meta-analyses of endoscopic band ligation versus nonselective beta-blockers in primary prophylaxis of variceal bleeding. Relative risk below 1.00 indicates advantage of endoscopic band ligation. Difference is statistically significant when CI does not cross the value of 1.

Author	No. of pts.	RR bleeding	CI for bleeding	RR mortality	CI mortality
Tripathi 2007	734	0.63	0.43–0.92	0.71	0.38–1.32
Gluud 2007	1167	0.59	0.41–0.77	1.02	0.75–1.39
Gluud 2007 (a)	324	0.86	0.55–1.35	1.22	0.84–1.78
Burroughs 2010	1364	0.50	0.37–0.67	0.94	0.70–1.28
Li 2011	1023	0.79	0.61–1.02	1.06	0.86–1.30

^aLimited to trials with adequate bias control.

Recently, it has been suggested to replace the traditional NSBB, propranolol or nadolol, with carvedilol, an NSBB which has a partial anti- α -2 adrenergic activity, which may be helpful in decreasing the enhanced intrahepatic venous vasoconstriction. Indeed, carvedilol was shown to be more effective in decreasing HVPG than propranolol,³¹ and to decrease HVPG in patients nonresponder to propranolol,³² although there are also some contrasting observations.³³ A single trial compared carvedilol to endoscopic band ligation in primary prophylaxis,³⁴ and showed a lower incidence of variceal bleeding in patients receiving carvedilol. Further studies are required to completely define this issue.

Only a few studies have investigated the possible advantage of the association of NSBB and band ligation in comparison to either treatment alone in the primary prophylaxis of variceal bleeding.^{35–37} A single study, the smallest in size³⁶ was favorable to the association, while two did not show any difference in the rate of esophageal bleeding, overall gastrointestinal bleeding, or death. The lack of advantage of the association in this indication contrasts with the results obtained in the prevention of recurrent variceal bleeding.^{38,39} This may be related to the different risk of bleeding in the two settings. Indeed, the combination of two effective treatments in the setting of primary prophylaxis, where the treatment is intended to prevent an event with a relatively low incidence, may have no benefit because the addition of the side-effects of the two treatments eventually balances out any possible therapeutic improvement.

At the consensus workshop of Baveno V⁷ it was concluded that either non-selective beta-blockers or band ligation are recommended for the prevention of a first variceal bleeding of medium or large varices, and the choice should be based on local resources and expertise, patients' characteristics and preference, side-effects and contraindications. In addition, a survey reported at the same workshop concluded that among the faculty members of the conference, two/third considered NSBB the best approach, and three quarters used NSBB as first option in their practice (Figure 3).

TREATMENT OF PATIENTS WITH CONTRAINDICATION OR SIDE-EFFECTS DUE TO BETA-BLOCKERS

Contraindications to beta-blockers in patients with portal hypertension are the same as in patients with different diseases. The major contraindications are reported in Table 3. To rule out possible contraindications, history, physical examination and standard ECG are sufficient.

In patients with contraindication, therapeutic options are limited. The use of long-acting nitrates alone has been suggested, based on the observation that in a single trial they were shown to be of similar efficacy as non-selective beta-blockers in patients without contraindications.⁴⁰

Figure 3 Preference between nonselective beta-blockers and endoscopic band ligation in the survey of the expert panel participating to the Baveno V consensus conference (2010). Panel A: answers to the question: “what do you consider the best approach for primary prophylaxis of variceal bleeding?”; panel B: answers to the question: “In your current clinical practice for primary prophylaxis, which is the first option?”.

However, in a trial especially designed to address this point, isosorbide mononitrate was not better than placebo in preventing bleeding or death after a follow-up of 2 years.⁴¹

Band ligation appears to be a suitable option, since it has been shown to be at least as effective as non-selective beta-blockers in several trials. The usefulness in patients with contraindications or side-effects due to beta-blockers is not so clearly demonstrated, as in patients who cannot be treated with the first line treatment, a lower efficacy is expected also with another treatment, because of co-morbidity, lower compliance, and further, poorly defined factors. Indeed, in a randomized trial of ligation versus no treatment in patients unable to take beta-blockers, Triantos⁴² showed disappointing results (5/25

Table 3 Contraindications to nonselective beta-blockers in portal hypertension.

- Heart failure
- A-V heart block
- Sinus bradycardia and other hypokinetic arrhythmias
- Chronic obstructive pulmonary disease; bronchial asthma
- Peripheral arteriopathy with trophic lesions
- Diabetes treated with insulin
- Demonstrated allergy for the drug

bleeds in the treatment arm versus 2/27 in the no treatment arm), which determined premature interruption of the trial. However, it should be observed that the difference in bleeding rate in this study was not statistically significant. At odds with the above results, Dell'Era et al⁴³ reported similar bleeding rates in patients with contraindications/intolerance to beta-blockers treated with band ligation compared to patients who were non-responders to beta-blockers and had been switched to band ligation. Combining these pieces of evidence, the Baveno V consensus conference concluded that these patients should be treated with band ligation.

CONCLUSIONS

- The prevention of the first bleeding is a cornerstone in the treatment of portal hypertension.
- Based on the patients' conditions and the features of the varices, there is a role for both pharmacological and endoscopic treatment.
- It is expected that patients will receive the best treatment in centers where both treatments are available with the same level of expertise.

CONFLICTS OF INTEREST

All authors have none to declare.

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