

Is pharmacological therapy the best choice for primary prevention of variceal hemorrhaging in patients with hepatic cirrhosis?

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Bleeding by esophageal varices represents one of the most catastrophic complications in a patient with hepatic cirrhosis. It is often the first form of liver decompensation due to this disease. In spite of improvement in survival rates over the last 20 years, and in spite of diminishing hospitalization rates, mortality for each episode of continuous variceal bleeding continues to be nearly 20% (1, 2). At the time of the initial endoscopy, 30% of Child A cirrhotic patients, and as many as 80% of Child C patients, have esophageal varices. The appearance of varices increases mortality rates after one year by 3.4% and increases bleeding rates by 57% in cirrhotic patients. A new proposal which classifies varices by stages from I to IV takes into account the presence of varices and bleeding, and then correlates them with mortality (3, 4) (See Table 1).

Table 1. Classification of stages and mortality for cirrhotic patients.

Cirrhosis Phase	Stage	Complication	Mortality
Compensated	I	No varices-no ascites	1%
	II	Varices-no ascites	3.4%
Decompensated	III	Varices + ascites	20%
	IV	Variceal Bleeding	57%

The systems currently in use for classification of varice sizes are subjective and have the potential for variations in classification according to the observer, variation that is accentuated when the observer is an inexpert endoscopist, as are the majority in daily practice. In addition, only 30% of patients fit the criteria of high risk for variceal bleeding (e.g. medium to large size varices, presence of red marks on varices and decompensated cirrhosis, Child B-C). The decision to initiate prophylaxis for bleeding varices rests potentially on the opinion of endoscopists with little experience and on risk factors that are present in less than 50% of patients. New noninvasive techniques as video-capsules and Computed Tomography cannot offer significant improvements in diagnostic sensitivity for varices (5, 6, 7). Accordingly, initiation of these preventive measures must be rationalized and strictly controlled in order to obtain the greatest benefit by diminishing costs and side effects.

At the present time, two strategies are in use to prevent hemorrhage by esophageal varices: elastic band ligation and pharmacological therapy, the latter of which is the topic of this presentation.

DRUGS USED IN PRIMARY PREVENTION OF VARICEAL BLEEDING

Since Lebrec's initial studies in the 1980s, non-cardio selective beta blockers (such as propranolol, nadolol and timolol) have been the basis for primary prevention of bleeding varices in cirrhotic patients. These drugs slow the heart beat and reduce cardiac output by acting upon B1 receptors in the heart. By acting on the B2 receptors of the splanchnic bed they generate a vasoconstricting alpha adrenergic response that reduces portal blood flow. In addition, increased resistance in the collateral vessels of the portal system (azygos vein) reduces blood flow and variceal pressure. Hence, beta blockers, unlike ligation, affect the main mechanism facilitating occurrence and rupture of varices, i.e. portal blood pressure. It is also possible that beta blockers diminish other complications related to portal hypertension including ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal syndrome, bleeding from gastric varices and hypertensive gastropathy. Administration of nitrates alone or added to beta blockers have not been demonstrated to be effective in the primary prevention of hemorrhaging and increase mortality rates in patients over 50 years of age (8, 9).

Response to treatment

Treatment response to beta blockers is measured by empirical observations such as a 25% reduction in cardiac frequency to a level of 55-60 heartbeats per minute. Since this does not have result directly in changed portal pressure, we can only reduce bleeding in 45% of patients (29% in non-treated vs. 14% in treated) with evident risk factors (10).

Although the Hepatic Venous Pressure Gradient (HVPG) is an indirect measure of portal pressure, it is the most objective form for evaluating the response to beta blockers. Nevertheless, it is an invasive technique which is not available in many centers. It also increases costs of handling cirrhotic patients with varices significantly, especially at the scene of primary prevention. Normal portal pressure measured by HVPG is less than 5 mmHg. When HVPG is over this value, it is clear that there is portal hypertension. A measurement over 10 mm Hg is defined as clinically significant portal hypertension at which point complications such as varices, ascites and encephalopathy start to appear. When HVPG is over 12 mm Hg, varices begin to rupture (11, 12).

Ideal pharmacological intervention reduces HVPG below 12 mm Hg or at least to 20% basal value. This is reached in 45% of total treated patients. The bleeding rate after two years is 4% for hemodynamic responders, rising to 10% after five years. In contrast the bleeding rate for

non-responsive patients after two years is 22%, rising to 45% after five years. Even for non-responsive patients, these numbers are significantly lower than the percentages of patients who do not receive treatment with beta blockers. Bleeding develops in 63% of these patients. Addition of nitrates improves this response in 8% of patients, but in no case is this medicine administered. This is due to the poor response and increased mortality rate in patients over 50 years. A group of partially responsive patients also exists. Their HVPG diminishes between 10% and 20% when beta blockers are administered. This group might benefit from a combination of beta blockers and ligation (13-15).

In spite of the above, there are no definitive studies endorsing routine use of HVPG measurement during primary prevention of variceal bleeding. Perhaps this is because it has been better established for acute bleeding (transjugular intrahepatic portosystemic shunt (TIPS) is indicated at HVPG > 20 mm HG) and in the prevention of recurrent bleeding (16).

Adverse events

An obstacle to the use of beta blockers is the frequency of adverse events (18%) that lead to the suspension of therapy for 30% of these patients. Most frequent among these events are hypotension, asthenia, fatigue, dyspnea, impotence, insomnia and difficulty concentrating. These indirect effects can be easily handled with dose adjustments or suspension of medication. An argument against beta blockers is related to the high rate of hospitalization due to bleeding episodes. Nevertheless, these appear months or years after suspension of medication and are not evident at the moment when a patient is offered the alternative of band ligation (8, 10, 17).

New drugs

Carvedilol, a potent non-cardio selective beta blocker with vasodilative properties related to alpha blockers, is a therapeutic which is more effective at reducing portal pressure (18). A recent study compared 77 patients who received a daily dose of 12.5 mg of carvedilol with 75 patients who had been ligated. The bleeding rate in the group treated with carvedilol was 10%, while the bleeding rate for the group which had undergone ligations was 23%. There was no significant difference in the mortality rates which were 35% and 37% respectively. Adverse effects appeared in 50% of the patients who received carvedilol. However, only 13% of these patients had to have medication suspended due to dyspnea, impotence, nausea, vomiting or symptomatic hypotension (19).

COMPARATIVE STUDIES OF DRUGS AND BAND LIGATURE

The two interventions currently available for primary prevention of variceal bleeding are elastic band ligation and beta blocker drug therapy. Derivative surgery is not used due to morbidity, associated mortality and to the difficulty that can be generated for any future transplant. Although the use of TIPS significantly lowers portal pressure, it also increases the frequency of severe adverse events such as untreatable encephalopathy, and it can precipitate hepatic insufficiency (20).

At least 16 studies comparing ligation to beta blockers have been published in 4 meta analyses (21, 22, 23, 24). The conclusion reached in these studies is that ligation is superior in prevention of the first episode of variceal bleeding without any effects on mortality. *Therefore, both types of intervention may be offered to patients as possible primary therapeutic options.*

There are differences in the methodologies of these studies that need to be properly studied.

1. Six (6) of the studies have been published in the form of summaries. After reviewing the 10 complete studies, no differences in bleeding rates were found among them (15% for ligation versus 22% for beta blockers).
2. Follow-up time varies among the studies. Studies with durations of more than 20 months showed no differences in prevention of hemorrhaging (18% for ligation versus 22% for beta blockers). Rates for studies which lasted less than 20 months were 8% for ligation and 22% for beta blockers.
3. Whether or not patients in these studies were randomized is not clear, and number of patients included in these studies may be insufficient.
4. Studies of the safety and effectiveness of beta blockers take more than 20 years while the long term safety of ligation is uncertain.
5. A recent study showed that patients may prefer ligation (64%). Nevertheless, severe potential adverse effects of ligation such as perforation and bleeding ulcers were not explained to patients in the study, nor were patients offered the option of changing to ligation in cases of intolerance to beta blockers (25).

Another study randomly assigned 52 patients who were incapable of taking beta blockers to ligatures (25 patients) or no treatment (27 patients). A greater number of bleeding episodes occurred among patients who had received band ligation, and the study had to be stopped prematurely (26). All these factors show that recommendations must be made with caution in order to offer the best alternative to patients.

Guideline Recommendations

Since the last Baveno IV meeting (27) guidelines for prevention and handling of variceal bleeding have been updated by the American Association for the Study of Liver Diseases (AASLD) on two opportunities (28, 29), once by the Asian Pacific Association for the Study of the Liver (30) and once by the Veterans Administration (31).

DEFINITION OF VARICES

- a. High risk esophageal varices: large (> 5 mm), with red markings (cherry red) hematocystic, with varice over varice, with decompensated cirrhosis.
- b. Low risk esophageal varices: small (< 5 mm), without red markings, with compensated cirrhosis.
- c. To be defined: small varices with red markings and/or advanced Child, and big varices without red markings and/or Child A.

ENDOSCOPIC SCREENING OF VARICES

- a. An endoscopy must be performed on every recently diagnosed cirrhotic patient.
- b. A cirrhotic patient without varices needs a follow-up every 2 to 3 years. If the patient is decompensated follow-ups must be more frequent (every 6 months).
- c. A compensated cirrhotic patient with small varices without red markings needs a follow-up every year.
- d. Primary prophylaxis should be initiated for cirrhotic patients with high risk varices.

PRE-PRIMARY PREVENTION

There is no current support for beginning prophylaxis with beta blockers in cirrhotic patients without varices. Adverse effects outnumber benefits, although there is still a subgroup of patients with HVPG < 10 mm of Hg at basal level which must be defined.

Early primary prevention

- a. Varices progress 5% to 12% annually.
- b. Beta blockers may prevent growth and/or bleeding of small varices.
- c. Cirrhotic patients with small varices, red marking and advanced Child should receive prophylaxis with beta blockers.
- d. There is no role for ligation in preventing the growth of varices.

Prevention of the first episode of variceal bleeding

- a. Primary prophylaxis reduces bleeding risk in patients with high risk varices.
- b. Band ligation and non-cardio selective beta blockers represent available alternative choices.
- c. Beta blockers reduce mortality and variceal hemorrhage risk better than placebo.
- d. Band ligation reduces bleeding risk, mortality from bleeding and global mortality better than placebo.
- e. Ligation is superior to beta blockers for preventing episodes of variceal bleeding but it has no advantages in terms of survival.
- f. Adding beta blockers to ligation does not augment efficacy.
- g. Mono-therapy with nitrates does not belong in primary prevention.
- h. Adding nitrates to beta blockers may further reduce portal pressure, but this does not result in diminished risk of bleeding.
- i. Cirrhotic patients with high risk varices can be treated with beta blockers (with HVPG monitoring if available) or with band ligation to prevent initial bleeding.

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