INTERNAL MEDICINE

NONSELECTIVE BETA-BLOCKERS IN PATIENTS WITH CIRRHOSIS: "THE THERAPEUTIC WINDOW"

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NONSELECTIVE BETA-BLOCKERS IN PATIENTS WITH CIRRHOSIS: "THE THERAPEUTIC WINDOW" (Abstract): For over 30 years, nonselective beta-blockers (NSBB) have been successfully used for preventing variceal bleeding in patients with cirrhosis and portal hypertension. Nevertheless, recent studies suggest that NSBB may be effective only within a particular "therapeutic window" in patients with advanced liver disease. Outside of this window, in early stages of cirrhosis and in very advanced cirrhosis, NSBB may be ineffective and even potentially harmful. In this paper we review the beneficial effects and potential harms of beta-blocker therapy in cirrhosis and underline the most recent recommendations for their use in very advanced cases of liver disease. Keywords: LIVER CIRRHOSIS; Beta-BLOCKERS; THERAPEUTIC WINDOW.

Pathophysiological basis for using nonselective beta-blockers (NSBB) in patients with cirrhosis. The development of portal hypertension in cirrhosis is mainly due to:

a) An increase in resistance to portal blood flow, because of architectural modifications in the liver, and
b) An increase in portal territory blood flow, due to splanchnic arteriolar vasodilation.

Therefore, NSBB goal in cirrhosis is to reduce portal pressure by two essential mechanisms:

a) β1-adrenergic blockade, which decreases cardiac output, leading to reduced portal blood flow, and
b) β2-adrenergic blockade, followed by an increase in arterial splanchnic resistance.

How did NSBB occur in the treatment of cirrhotic patient. The study of Lebrec et al. (3) published in 1981 in New England Journal of Medicine was the key-point in establishing the role of NSBB in the secondary prevention of variceal hemorrhage.

In 1987, the study of Pascal et al.(4) underlines the role of NSBB in the primary prophylaxis of variceal bleeding.

In 1991, Poynard et al.(5) meta-analysis together with other studies establishes that NSBB represent the first line therapy both in primary and in secondary prophylaxis of variceal hemorrhage.

The most important studies supporting NSBB usage in the treatment of cirrhotic patient are summarized by Phillip S. Ge., in
The indications of NSBB in cirrhosis

1. Primary prevention of variceal hemorrhage:
   a) In cirrhotic patients with medium or large esophageal varices, NSBB lower the risk of first variceal bleeding (from 30% to 14%, compared to placebo) (6).
   b) Primary prevention is not recommended in cirrhotic patients without esophageal varices, whatever the value of hepatic venous pressure gradient (HVPG).

2. Secondary prevention of variceal hemorrhage: NSBB reduce the rate of variceal rebleeding from 60% to approximately 40%.

3. Other benefits: NSBB might prevent the development of spontaneous bacterial peritonitis (SBP), by reducing intestinal permeability and bacterial translocation.

I. Pre-primary prophylaxis (to prevent the development of esophageal varices)

There are no data to confirm the benefit of using NSBB to prevent the development of esophageal varices, the most efficient method being the treatment of liver disease.

Studies showed that in patients without esophageal varices, NSBB (like timolol) have no role in preventing the development of esophageal varices, and the side effects are more frequent (7).

In conclusion, NSBB are not recommended in this set of patients.

II. Primary prevention (the prevention of first episode of variceal bleeding)

An important meta-analysis of 11 trials including almost 1200 patients evaluated the role of NSBB (propranolol or nadolol) in the primary prophylaxis of variceal haemorrhage (8).

The results showed that in cirrhotic patients with medium or large esophageal varices NSBB lower the risk of first variceal bleeding (from 30% to 14%, compared to placebo) (6).

Other studies show that one bleeding episode is avoided for every ten patients treated with NSBB. In conclusion, NSBB reduce the rate of bleeding-related mortality compared to the control group (9).

Upon the size of esophageal varices, the recommendations are as follows:

According to Baveno VI Consensus, in cirrhotic patients with medium or large esophageal varices NSBB are recommended to prevent the first episode of variceal hemorrhage (6).

Still, the risk of bleeding depends not only upon the size of esophageal varices, but also upon the presence of the marks of bleeding (“red signs”) on the varices and on the severity of liver disease.

In patients with compensated liver disease (Child-Pugh A) and small esophageal varices without red signs, the risk of bleeding is 6%, while the patients with Child-Pugh C cirrhosis, with large esophageal varices with red signs have a risk of bleeding of 76% (10).

The set of cirrhotic patients with small esophageal varices are classified in two groups depending on the other factors which influence the risk of bleeding:

1. In patients with small esophageal varices and low risk of bleeding, which means without red signs and in the absence of severe liver disease (CHILD A), there are insufficient data that the use of NSBB would prevent the progression of esophageal varices. These patients may use NSBB to prevent the esophageal haemorrhage just in some individualized cases. The patients with small esophageal varices without therapy with NSBB must have endoscopy every 2 years, to evaluate the progression of
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esophageal varices (11-13).

2. In cirrhotic patients with small esophageal varices and high risk of bleeding, meaning the presence of red signs and/or the presence of severe liver disease (CHILD-PUGH B or C), the treatment with NSBB is recommended (6,13).

III. Secondary prophylaxis of variceal bleeding

Secondary prevention means the prevention of rebleeding from esophageal varices, being addressed to those cirrhotic patients who have already had an episode of variceal haemorrhage.

Studies showed that patients who survive an episode of variceal haemorrhage have a high risk of rebleeding and death. In this set, untreated patients have a rebleeding rate of 60% at 1-2 years, with a mortality of 20-50% (14).

Besides, the prevention of rebleeding from esophageal varices was the first confirmed indication for using NSBB in the treatment of cirrhosis (the study of Lebrec et al. from 1981) (3).

It was demonstrated in trials that NSBB reduce the rebleeding rate from 60% to almost 40% (3,5,8).

According to the last guidelines, the combination of NSBB and band ligation is considered the maximal therapy for preventing rebleeding from esophageal varices. This provides the lowest rates of rebleeding, without major differences between the survival rates (compared to the patients treated only with NSBB). The early administration of NSBB may reduce the risk of bleeding till endoscopic band ligation. (6,15).

Other benefits of NSBB in cirrhosis include the prevention of other complications, like bleeding from portal gastropathy, the occurrence of ascites and of SBP (3,17).

The control of the efficiency of NSBB in cirrhosis targets:

a) A hemodynamic response to NSBB means a decrease in the HVPGE below 12 mmHg or of 20% of the baseline value;

b) The adrenergic response to NSBB is defined as a decrease in the heart rate (measured 12-24 h after drug administration) of 25% of the baseline value;

c) The dose of NSBB is decided according to: a decrease in the heart rate (HR) of 25% of the basal value; the value of HR at rest not below 55/min; pay attention to the occurrence of side effects (3).

The side effects of NSBB

a) Cardiac: the exacerbation or precipitation of heart failure, symptomatic bradycardia, high grade heart block. The acute withdrawal of beta-blocker therapy can lead to accelerated angina, myocardial infarction and sudden death!

b) Pulmonary: increased airways resistance in patients with bronchospasm

c) Circulatory: the exacerbation of peripheral artery disease (claudication, absent pulses, cyanosis and gangrene)

d) Metabolic: in patients with diabetes mellitus, risk of severe insulin-induced hypoglycemia

e) Other: depression, fatigue and sexual dysfunction.

Contraindications to NSBB in cirrhotic patients

These may be classified as follows:

1) General contraindications

a) Absolute – severe heart failure, advanced heart block;

b) Relative – moderate chronic heart failure, asthma, chronic obstructive pulmonary disease, peripheral arterial disease, Raynaud syndrome, insulin-treated diabetes mellitus.
2) *Cirrhosis-related contraindications*
   a) Portopulmonary hypertension;
   b) Refractory ascites.

**Is the therapy with NSBB in cirrhosis safe? How did this question occur?** The same authors whose studies established the use of NSBB in the treatment of cirrhosis raised this problem!

In 2010, the study of Serste et al. (17,18) published in Hepatology concluded that NSBB should be contraindicated in cirrhotic patients with refractory ascites, leading to a shortening of survival.

Other authors, Wong and Salerno (19) showed that, regardless the design of the study, the safety of the treatment with propranolol in cirrhotic patients with refractory ascites is a problem.

In 2011, another trial of Lebrec et al. (3) postulated that NSBB are associated with the paracentesis-induced circulatory dysfunction (PICD), leading to a reduced survival rate in this group of patients.

"*The therapeutic window*” hypothesis. Recent studies of Krag et al. (20) suggest that the efficiency of NSBB manifests just during a window in the disease, named "therapeutic window”, in those patients with advanced cirrhosis.

Outside of this window, the therapy with NSBB may be ineffective in early stages of cirrhosis and potentially harmful in advanced cirrhosis (1).

**Defining the term of ”the therapeutic window”.** In early stages of cirrhosis, NSBB have no beneficial effect on survival and the adverse events may be more frequent (7).

These stages are defined by the following parameters: the esophageal varices are small or absent; intact cardiac reserve; sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) have baseline activity; the risk of gut bacterial translocation is low, and the risk of mortality is also low (7).

In decompensated cirrhosis, NSBB improves the survival rate, lowering the rate of esophageal bleeding and of bacterial translocation.

This stage of cirrhosis has the following characteristics: medium or large esophageal varices; ascites; the cardiac reserve is intact, but declining; SNS and RAAS have increased but not maximal activity, and the risk of bacterial translocation and of mortality are increased (1).

The final (terminal) stages of cirrhosis are characterized by refractory ascites; impaired cardiac reserve, with baseline hypotension; SNS and RAAS are maximally stimulated and can no longer maintain adequate blood pressure (BP); high risk of gut bacterial translocation and of mortality (7).

In these stages, NSBB decrease the rate of survival as a result of the negative impact on cardiac reserve, lowering the perfusion of vital organs and precipitating the hepatorenal syndrome (HRS).

**Why NSBB are not indicated in refractory ascites?** The study of Serste et al. (18) from 2011 show that in cirrhotic patients with refractory ascites NSBB may cause a higher risk of paracentesis-induced circulatory dysfunction, thus reducing the rate of survival (2). NSBB (like propranolol) would prevent the adaptive hemodynamic response after large volume paracentesis, subsequently inducing PICD.

**The factors which close the ”therapeutic window” are:**
   a) The occurrence of refractory ascites and of SBP;
   b) Systolic BP below 95 mmHg;
   c) The presence of symptoms of orthostatic hypotension;
d) The occurrence of septic episodes;
e) Increased levels of serum creatinine.

The presented data show that the presence of medium or large esophageal varices opens the window of opportunity, which will be closed by the occurrence of refractory ascites, decreased medium BP and/or HRS. Taking into consideration the duration relatively limited of the "therapeutic window", some authors agree that NSBB should not be recommended in patients with low medical compliance and/or poor medical follow-up (21,22).

The initiation and continuation of NSBB therapy is ideal in those patients with home monitoring of BP and HR and who will have a close follow-up meaning frequent medical visits (23).

Concerning the "therapeutic window" hypothesis, the results from studies and the existing evidences are still conflicting.

For example, the study of Galbois et al. (24) published in Hepatology contradicts some of the previous data, suggesting that NSBB are not associated with an inadequate hemodynamic response in patients with cirrhosis and severe sepsis.

For now, the recommendations of Baveno VI Consensus (6) are the following:

1) The safety of beta-blockers administration in cirrhotic patients with refractory ascites and/or hepatorenal syndrome was not demonstrated;
2) The patients with refractory ascites must be intensively monitored; if systemic hypotension or azotemia occur, we must reduce the dosage of NSBB or even discontinue the BB therapy;
3) If NSBB therapy is discontinued, the patient will need esophageal band ligation for preventing variceal bleeding;
4) Until practical data from randomised trials arrive, NSBB must be discontinued or the dose must be reduced in patients with refractory ascites if: systolic BP is below 90 mmHg; serum creatinine is raising and/or hyponatremia below 130 mmol/l occurs;
5) The consequence of discontinuing the BB therapy on the prevention of esophageal bleeding is not known;
6) If variceal bleeding or SBP occur after discontinuing the BB therapy, we may restart the treatment if the above parameters became normal.

CONCLUSIONS

In conclusion, the therapy with NSBB requires special attention in two clinical settings:

a) Decompensated cirrhosis in terminal stage, and
b) Refractory ascites.

It remains unclear if, after closing the "therapeutic window" of NSBB in cirrhosis, this would be a definitive closure or not, referring to the possibility of restarting the beta-blocker medication after a period of time.

REFERENCES


