

Use of non-selective beta blockers in cirrhosis: The evidence we need before closing (or not) the window

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pressure gradient (HVPG) below 12 mmHg or at least 20% of the basal value. Nevertheless a relevant number of patients who do not achieve this HVPG reduction during NSBBs therapy do not bleed during follow up; this evidence suggests an additional non-hemodynamic advantage of NSBBs treatment to modify the natural history of cirrhosis. Recent studies have questioned the efficacy and safety of NSBBs in patients with advanced stage of liver disease characterized by refractory ascites and/or spontaneous bacterial peritonitis. These studies have suggested the existence of a defined and limited period to modify the natural history of cirrhosis by NSBBs: the "window hypothesis". According with this hypothesis, patients with cirrhosis benefit from the use of NSBBs from the appearance of varices up to the development of an advanced stage of cirrhosis. Indeed, in patients with refractory ascites and/or spontaneous bacterial peritonitis the hemodynamic effects of NSBBs may expose to a high risk of further complications such as renal insufficiency and/or death. Methodological concerns and contrasting results counterbalance the evidence produced up to now on this issue and are the main topic of this editorial.

Key words: Bleeding prophylaxis; End stage liver disease; Non-selective beta blockers; Portal hypertension; Cirrhosis

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Core tip: Non selective beta blockers (NSBBs) treatment in cirrhotic patients is an undisputed strategy for bleeding prophylaxis. Nevertheless recent studies question the efficacy and safety of NSBBs in patient with advanced cirrhosis, particularly in case of refractory ascites and spontaneous bacterial peritonitis. These results suggest that NSBBs have beneficial effects on cirrhosis only in a determinate phase of the liver disease: "window hypothesis". In our opinion, the evidence produced up to now is by far conclusive to contraindicate NSBBs in patients with advanced cirrhosis.

Abstract

Non selective beta blockers (NSBBs) are used in primary and secondary prophylaxis of portal hypertension-related bleeding in patients with cirrhosis. The efficacy of NSBBs treatment is predicted by hemodynamic response in term of reduction of the hepatic venous

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INTRODUCTION

Since their introduction to reduce the re-bleeding risk in-patients with cirrhosis^[1], the therapy with non-selective beta blockers (NSBBs) has been widely tested to successfully manage the risk of complications of portal hypertension (PHT) ranging from the first evidence of varices up to the bleeding related mortality^[2-5]. Moreover, therapy with NSBBs has been tested to prevent other complications such as the *de novo* appearance or worsening of ascites, spontaneous bacterial peritonitis (SBP), hepato-renal syndrome (HRS), and hepatic encephalopathy^[2-6].

The hepatic venous pressure gradient (HVPG), the difference between the wedged and the free hepatic venous pressures, measured by hepatic vein catheterization, is one of the most reliable surrogate markers of clinical outcome in patients with chronic liver disease^[7]. A HVPG ≥ 10 mmHg is independently associated with the appearance of esophageal varices and/or ascites in patients with cirrhosis, whereas a HVPG ≥ 12 mmHg is the threshold for the risk of variceal rupture and bleeding^[8]. Recently, investigators of PHT proposed a functional classification of cirrhosis according with a progressive multistage mortality risk^[9,10]. In line with this patient stratification, the one-year mortality after a variceal bleeding episode is 40%. This risk can be reduced by the chronic treatment with NSBBs^[11] mainly in patients achieving a significant reduction of HVPG^[2,3].

The therapy with NSBBs was based on the recognition that a hyperkinetic circulation is behind the development of symptoms of PHT. This circulatory state is maintained by a persistent vasodilation of the splanchnic arterial bed with reduction of the central blood volume, increased heart rate and cardiac output, and retention of sodium and fluids by the kidney^[12]. The reduction of this hyperkinetic circulation is the main target of therapy with NSBBs for cirrhotic patients. Indeed, the blockade of beta-1 receptors antagonizes the high cardiac output, whereas the blockade of beta-2 receptors allows the alpha-adrenergic tone to blunt the splanchnic arterial vasodilation with a lowering effect on portal pressure. Therefore, these pharmacodynamic effects can prevent a rupture of varices. A reduction of the HVPG below 12 mmHg or at least 20% of its basal value (hemodynamic response) under NSBBs is a highly specific predictor of protection from variceal rupture (good clinical response). Conversely, patients

who do not achieve this HVPG reduction despite NSBBs therapy (hemodynamic non-responders) are at the highest risk of variceal rupture, although up to 48% of them does not bleed during a relatively large period of time^[13]. This unexpected behavior could be explained assuming that these non-bleeding patients are protected by NSBB therapy even if they do not obtain the sufficient reduction of portal pressure. A few of other hemodynamic and non-hemodynamic effects of NSBB have been evoked to justify this clinical advantage^[13]. Among them, the ability of NSBBs to reduce the gastro-intestinal permeability to bacterial by-products is a favorable effect that occurs in both hemodynamic responders and non-responders^[14]. This is a crucial issue because the ability to cross intestinal barrier by bacteria and by bacterial by-products [bacterial translocation (BT)] is the main risk factor for the SBP, that in turn is the main trigger of HRS.

The efficacy of NSBBs in preventing SBP has been shown by Turnes *et al.*^[3] who demonstrated that a partial reduction of HVPG (11% instead of 20%) during NSBB therapy was enough to reduce the risk of SBP for a long period of time; while the meta-analysis made by Senzolo *et al.*^[15] including data from 5 studies, confirmed that the treatment with NSBBs reduces the risk of SBP.

Recently the French group who demonstrated, for the first time, the efficacy of NSBBs therapy to prevent variceal rupture, published a retrospective cohort study of 151 patients with refractory ascites finding that the treatment with NSBBs was independently associated with mortality [hazard ratio (HR) = 2.61 times, 95%CI: 1.91-3.44]^[16]. A similar concern for the safety of patients was raised for the risk of developing post-paracentesis circulatory dysfunction (PPCD) after large volume paracentesis^[17]. In addition, Mandorfer *et al.*^[18] reported the outcome of 182 incidental cases of SBP where the chronic treatment with NSBBs ($n = 86$) had exposed to an elevated cumulative risk of renal failure, either defined with the criteria of HRS (11% vs 24%, respectively) either defined as acute kidney injury, AKI (8% vs 20%, respectively).

All these observations fostered the hypothesis that patients with cirrhosis and PHT may take advantage from the therapy with NSBBs only if they fall in a well-defined window of the natural story of the disease. This window would be opened by the first appearance of esophageal varices at risk of bleeding and would be closed by the development of refractory ascites or other severe complications like SBP/HRS that are clinical hallmarks of an advanced liver disease^[19].

The observation by Ruiz-del-Arbol *et al.*^[20] that patients with SBP develop renal failure in association with reduction of cardiac output and mean arterial pressure can explain why NSBB therapy would be detrimental for survival of patients with advanced cirrhosis. This study and other similar evidences induced authors to revise the "theory of peripheral vasodilation" adding to the well-known algorithm a final

stage including patients characterized by a hyperkinetic circulation that slows down as a consequence of a relative failure of cardiac output^[21]. Accordingly, the inotropic and hypotensive effects of NSBBs could represent a danger for patients with advanced cirrhosis and refractory ascites and/or HRS. By contrast, many other investigators continue to prescribe NSBBs to patients with advanced cirrhosis sustaining that the methodological quality of these recent papers is not enough to making the results reliable^[22].

Therefore, the use of NSBBs in patients with advanced cirrhosis has become an issue of debate between those who are concerned upon the safety of NSBBs given to patients with severe cirrhosis and those who critics the quality of the methods used to generate the evidence of negative effects of NSBBs in cirrhosis. The methodological quality of the evidences reported in the papers of Serstè *et al.*^[17] and Mandorfer *et al.*^[18] may be too weak for such an important change of treatment in patients with cirrhosis. Indeed a series of flaws can be evidenced and summarized as following: (1) the lack of randomization to the treatment; (2) the retrospective nature of data collection; and (3) the insufficient number of patients included in the final analysis (not always consecutive).

It is noteworthy that patients developing HRS and/or SBP under NSBB therapy are those not totally protected by this class of drugs, in other words, they are clinically non-responders to NSBBs since they develop an event whose risk is reduced by the chronic treatment with NSBBs^[2,3]. Therefore, this cohort of patients constitutes a highly selected subgroup of cirrhotic patients with high mortality risk if not transplanted. Recently, Leitehad *et al.*^[23] conducted an observational study to explore whether or not the treatment by NSBBs increases the mortality risk of patients with an advanced liver disease. The study included a series of 322 consecutive candidates to liver transplant, 117 had refractory ascites. At exception of the window hypothesis, the survival analysis disclosed a significant mortality reduction for patients receiving NSBBs. This occurred in both categories of patients: those without refractory ascites ($HR_{mortality} = 0.55$; 95%CI: 0.32-0.95), and those with refractory ascites ($HR_{mortality} = 0.35$; 95%CI: 0.14-0.86). Noteworthy, the survival advantages were achieved even though patients under NSBBs had a low systemic arterial pressure. Moreover, possible selection biases were controlled by matching the population according with the propensity risk score. These results contradict the opinion that NSBBs are detrimental in patients with an advanced or end-stage liver disease. However, Authors fairly state that their patients were highly selected since they were candidates to liver transplantation.

In conclusion: which is the truth? Since its introduction, the evidenced based approach was used to test the efficacy of drugs against hard clinical end-points such as mortality, in order to replace the empiric approach. The randomized controlled trial (RCT) is the best tool

to minimize confounding factors and effect modifiers behind the apparent association between an exposure (e.g., treatment with NSBBs) and an effect (mortality) in a specific clinical setting (patients with advanced liver disease).

The studies supporting the "window hypothesis" challenge a huge amount of papers that consistently demonstrated the beneficial effect of NSBBs in patients with PHT. Therefore, it is now mandatory solving any doubts on the safety of such class of drugs in patients with advanced cirrhosis. This aim should be pursued by a trial including a sufficient number of patients on chronic NSBBs therapy with advanced cirrhosis, such as patients with SBP. The effects of the NSBBs would be compared randomizing these patients to stopping or not the chronic treatment with NSBBs. The preference of patients with SBP for such a trial would be justified by the relatively homogeneity of these patients ensured by objective criteria of diagnosis and high risk of renal failure. Certainly this kind of RCT is demanding, and needs a multicenter cooperation. However, the evidence we will obtain is essential before closing (or not) the window.

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