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Review

The 35-year odyssey of beta blockers in cirrhosis: any gender difference in sight?

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ABSTRACT

Cirrhosis is the end-stage of chronic liver disease and leads to the development of portal hypertension and its complications such as esophagogastric varices. Non-selective beta blockers (NSBB) are the keystone for the treatment of portal hypertension since the 1980s and, over the decades, several studies have confirmed their beneficial effect on the prevention of variceal (re)bleeding. Pharmacological studies showed effects of gender, sex hormones, oral contraceptives, and pregnancy on cytochrome P450 (CYPs) enzymes that metabolise NSBB, suggesting that gender differences might exist in the effect of NSBB. In this review, we focused on the 35-year knowledge about the use of beta blockers in cirrhosis and potential gender differences. We specifically examined the role of NSBB in pre-primary, primary and secondary prophylaxis of variceal bleeding, compared two commonly used NSBB (i.e., Propranolol and Carvedilol), and present the current controversies about the window of treatment in advanced cirrhosis with a specific focus on gender differences in NSBB effects. NSBB are not currently recommended in pre-primary prophylaxis of varices mainly because of lack of proven efficacy. On the other hand, NSBB are strongly recommended in patient with cirrhosis as primary (as alternative to endoscopic band ligation, EBL) and secondary prophylaxis (in addition to EBL) of variceal bleeding. To date, no studies have focused specifically on the effect of gender on NSBB treatment. Data extrapolated from clinical studies show that gender was neither a risk factor for the development of varices nor associated with a different response to treatment in primary or secondary prophylaxis. According to the available guidelines, no different, gender-based treatment for portal hypertension is recommended.

Contents

Abbreviations: HVPG, hepatic venous pressure gradient; NSBB, non-selective beta blockers; EBL, endoscopic band ligation; CYP, Cytochrome P450.

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1. Introduction

Cirrhosis is the end-stage of chronic liver diseases, such as chronic viral hepatitis, autoimmune hepatitis, alcoholic and non-alcoholic steatohepatitis. Chronic liver injury leads to the deposition of extracellular matrix and successively, to the formation of fibrotic septa and nodular structures in the hepatic parenchyma [1]. Portal hypertension is caused by increased intrahepatic vascular resistance to portal flow secondary to fibrosis, narrowing and compression of the hepatic sinusoids that leads to arterial splanchnic dilatation, increased venous collateral blood flow and hyperdynamic circulation [2]. The hepatic venous pressure gradient (HVPG) now is considered the gold standard for the measurement of portal pressure. Portal hypertension is defined as a HVPG >5 mmHg [3,4], whereas a HVPG >10 mmHg defines clinically relevant portal hypertension, which is the threshold for the development of complications such as esophagogastric varices, ascites, and hepatic encephalopathy [5]. Varices are present in approximately 50% of patients with cirrhosis [6,7] with an annual incidence rate of about 5–10%. The rate of progression of small varices to large varices has been reported to be 12% at 1 year and 31% at 3 years [8,9]. The incidence of first variceal bleeding is approximately 12–15% per year [9]. Despite improvements in the treatment of variceal bleeding, the high mortality rate associated with the bleeding (15–20%) seriously affects the prognosis of patients with cirrhosis [9,10].

For about 35 years, non-selective beta blockers (NSBB) have been used in the treatment of portal hypertension in order to prevent variceal bleeding. Their proven efficacy in primary and secondary prophylaxis of variceal bleeding is acknowledged by current national and international guidelines. Interestingly, although gender differences have been shown in susceptibility and progression of e.g., autoimmune and alcoholic liver diseases and in the metabolism of NSBB, very little is known about gender differences in the effect of NSBB on portal hypertension and its complications [11,12].

In this paper we will review the current knowledge and controversies about the use of beta blockers in portal hypertension, windows for treatment and potential gender differences in the effect of beta blockers on portal hypertension.

2. Beta blockers in portal hypertension

Non-selective beta blockers (NSBB) play a pivotal role in the treatment of portal hypertension. The first paper that showed the beneficial effect of NSBB in the prevention of variceal bleeding was a French study published in 1981 by Lebrec et al. [13]. This study analysed the risk of re-bleeding of 74 patients who were randomized to either placebo or oral Propranolol after the first episode of variceal bleeding. The percentage of patients without re-bleeding at 1-year was higher in the Propranolol group (96%) than in the placebo group (50%). A multicentre randomized controlled single-blinded trial in 1989 showed that the percentage of patients free of bleeding was significantly higher in the group treated with NSBB than in the placebo groups (83% vs. 61%) [14]. Several studies have confirmed, over decades, the beneficial effect of NSBB on the prevention of variceal (re)bleeding [15–17].

Baveno VI is the most important guideline on the use of NSBB for the management of variceal bleeding in portal hypertension and specified for pre-primary, primary and secondary prophylaxis, as summarized in Fig. 1. No gender-related recommendations are made [18]. Pre-primary prophylaxis refers to measures aimed at preventing the development of varices, whereas primary prophylaxys aims to prevent the first episode of variceal bleeding in subjects with endoscopically proven esophageal varices. Secondary prophylaxis aims to prevent further episodes of bleeding in subjects who have had already an episode of variceal bleeding [18].

Studies on the pre-primary prophylaxis, thus aiming to prevent the development of esophageal varices, have shown conflicting results. Old pathophysiological data on rat models with portal hypertension suggested a role of NSBB in preventing the development of varices, while more recent data in cirrhotic rats could not confirm this hypothesis [19–21]. Studies in humans showed that treatment with NSBBs cannot prevent the development of varices [22–25]. A meta-analysis on pre-primary prophylaxis with NSBB in subjects with portal hypertension showed no differences between NSBB and placebo, neither in the development of varices (OR = 1.05, 95%CI 0.25–4.36, p = 0.95) nor in variceal bleeding (OR = 0.59, 95%CI 0.24–1.47, p = 0.95) or mortality (OR = 0.70, 95%CI 0.45–1.1, p = 0.12) [26]. At multivariate analysis, female gender was not a risk factor for the development of varices [26]. Thus, NSBB in pre-primary prophylaxis of variceal bleeding is currently not recommended, mainly because of lack of efficacy [27].

Primary prophylaxis intends to prevent variceal bleeding in those patients who already have developed varices. In the case of low-risk varices, i.e. small-size varices in compensated cirrhosis, it is debated in as much treatment with NSBB can prevent the progression of varices [24,25,28,29]. Current guidelines do not give clear recommendations for this group of patients, it could be considered a to commence a treatment with NSBB or to endoscopically re-evaluate varices after 1 or 2 years [18]. Rather, subjects with clinically significant portal hypertension and presence of high-risk varices (large/medium varices, presence of red wale marks) should undergo primary prophylaxis either with NSBB or with endoscopic band ligation (EBL) [18]. NSBB have been compared with EBL in a number of clinical trials [24,30–33]. In 2012, a comprehensive Cochrane Review concluded that the incidence of bleeding was not different in patients treated with either NSBB or EBL (12% vs.17%) and that there also were no differences in bleeding-related mortality between the two treatment groups (5.1% vs. 6.3%) [34].

Cirrhotic patients with a previous variceal bleeding have a 60% risk of re-bleeding in 2 years [35]. Secondary prophylaxis intends to prevent variceal re-bleeding. For this purpose, it is recommended to use NSBB in combination with repeated sessions of EBL until complete eradication of varices [18,36], in particular, as recent 2- and 7-year follow-up data showed no differences on re-bleeding rates in patients treated solely with either NSBB or EBL [31]. Of note, NSBB showed slightly increased survival after 2-year follow-up [31]. Only few clinical trials on NSBB in secondary prophylaxis examined a potential gender effect on the incidence of re-bleeding or survival. These did not show any such effect in most of them while only one study revealed a small protective effect of female gender (Table 1) [31,37–43].

2.1. NSBB compared: Propranolol vs. Carvedilol

NSBB reduce portal hypertension by acting on β-1 receptors, leading to reduced cardiac output and splanchnic blood flow, and on β-2 receptors, leading to splanchnic vasoconstriction [44]. Propranolol was the first one used and the most widely studied, but some evidences have pointed towards the use of Carvedilol as a reliable and potentially even more efficient treatment [45]. Propranolol is a non-selective β-1 and β-2 blocker [46] whereas Carvedilol in addition to a strong non-selective β-1/β-2 also has a weak α-1 receptor blocking activity, thus adding a weak vasodilating activity that improves vascular resistance in the liver through the local release of nitric oxide [47,48]. Pharmacodynamic and pharmacokinetic characteristics of Propranolol and Carvedilol are shown in Tables 2 and 3, respectively.

In cirrhotic rats, Carvedilol also improved liver inflammatory response, oxidative stress and fibrosis [49]. Thus, Carvedilol might