

Non-Selective Beta-Blockers in Liver Cirrhosis: Friends or Foes? A Review of the Literature

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ABSTRACT

Cirrhosis has become a leading cause of death in the United States and worldwide owing to the increased prevalence of alcoholic liver disease, hepatitis C, and more recently, non-alcoholic steatohepatitis and non-alcoholic fatty liver disease. Beta-blockers have been proven to be efficacious in primary, as long as secondary prophylaxis of variceal bleeding, more than 35 years ago. Nonetheless, recent data has cautioned the use of beta-blockers in patients with end-stage cirrhosis and refractory ascites suggesting increased mortality from beta-blockers in this group of patients. In this article, we will discuss this topic in details, and review the conflicting studies about beta-blockers

in cirrhosis, and try to provide logical suggestions concerning the use of this class of medication in patients with cirrhosis.

Key words: Non-Selective Beta-Blockers; Liver Cirrhosis; Portal Hypertension; Oesophageal Varices Bleeding; Refractory Ascites
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Abbreviations: Non-Selective Beta-blockers (NSBB); Non-Alcoholic Steatohepatitis (NASH); Non-Alcoholic Fatty Liver Disease (NAFLD); Mean Arterial Pressure (MAP); Endoscopic Variceal Ligation (EVL).

INTRODUCTION

Cirrhosis is becoming a leading cause of mortality and morbidity worldwide^[1,2], and since 1981, beta-blockers were found to be highly efficacious in both, primary and secondary prevention of variceal bleeding^[3]. Non-selective beta-blockers (NSBB) became the cornerstone of the medical treatment of patients with cirrhosis^[3], and this was demonstrated in several solid studies. However, recent evidence has questioned the use of beta-blockers in patients with end-stage liver disease and refractory ascites^[3]. In this article, we are going to review almost all the previous studies about beta-blocker therapy in patients with cirrhosis, and find out the beneficial effects of this therapy, its potential complications and harms, and try to provide suggestions regarding its appropriate use in this specific category of patients.

CIRRHOSIS

Cirrhosis represents an advanced stage of progressive hepatic fibrosis characterized by distortion of the hepatic architecture and the formation of regenerative nodules. It is normally considered to be irreversible in its late stages at which point the only therapeutic

option may be liver transplantation, and lately it is becoming a leading cause of mortality in the United States and worldwide^[3]. The leading causes of cirrhosis comprise alcoholic liver disease, hepatitis C & B, and recently, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH)^[3].

Cirrhosis is not only a cause of mortality but also a cause of morbidity and it may alter the lifestyle of the patients, especially when complications start to occur such as ascites, spontaneous bacterial peritonitis, variceal hemorrhage, hepatic encephalopathy, and cardiomyopathy, among others. Beta-blockers were found to be the cornerstone in the management of patients with cirrhosis. This article will review the role of beta-blocking therapy in reducing the complications of cirrhosis in general, and variceal hemorrhage in particular.

BETA-BLOCKERS

Beta-adrenergic blockers are a central class of drugs for the treatment of various heart diseases such as high blood pressure^[4], angina pectoris^[5], cardiac arrhythmias, hypertrophic cardiomyopathy, and heart failure^[6], among others. Similarly, these agents are used to treat extra-cardiac diseases such as migraine and glaucoma^[7], and in the 1980s they were introduced in the treatment of variceal hemorrhage in patients with cirrhosis and portal hypertension^[8-11].

What is a beta-blocker?

Catecholamines are hormones released from the sympathetic nervous system and they stimulate adrenergic receptors on cell surface enabling the body to withstand stress, anxiety, and exercise^[7]. Beta-adrenergic receptors are found in the heart, lungs, and blood vessels, and the stimulation of these receptors causes an increase in heart rate, heart muscle contraction, blood pressure, and relaxation of smooth muscle in the bronchial tubes in the lungs^[7]. However, beta-blocking drugs will block the access of catecholamines to their receptors so that the heart rate and blood pressure are reduced. This, in turn, will decrease the oxygen needs of the heart^[7].

The beta-blocking drugs

In the United States, there are 16 beta-blockers available^[7]. All of them block the effects of catecholamines at the level of the heart, but they differ to a certain degree in their ability to block receptors in the blood vessels and lungs^[7]. Selective beta-blockers are the ones with major actions on the heart such as atenolol, metoprolol, betaxolol, bisoprolol, and esmolol. Non-selective beta-blockers are the ones that block the receptors in the heart and in the blood vessels; among these drugs are nadolol, propranolol, sotalol, and timolol. Finally, some beta-blockers, in addition of their beta-blocking ability, have an alpha-blocking property and they may cause further dilatation in the

blood vessels and hypotension. These are carvedilol and labetalol^[7].

BETA-BLOCKERS IN CIRRHOSIS

In the early stages of cirrhosis, patients may be asymptomatic. As the disease advances, portal hypertension start to develop leading to ascites, hepatic encephalopathy, and variceal hemorrhage^[12]. Other hemodynamic changes occur in cirrhosis starting with peripheral arterial vasodilatation from reduced systemic vascular resistance which is the most widely accepted hypothesis, leading to arterial underfilling and increased heart rate and cardiac output, and activating the salt-retaining mechanisms such as the sympathetic nervous system and the renin-angiotensin-aldosterone system to counteract low arterial blood pressure^[13-16]. It is in this pathophysiological context that beta-blockers have theoretical benefits, first by reducing cardiac output via beta-1 adrenergic blockade, and second, by reducing portal blood flow via beta-2 adrenergic blockade and splanchnic vasoconstriction^[17]. Moreover, independently of their hemodynamic effects, treatment with beta-blockers decreased intestinal permeability and significantly reduced the risk of spontaneous bacterial peritonitis in both hemodynamic responders and non-responders^[18].

The benefits of beta-blockade therapy were demonstrated in several solid studies as shown in table 1 below. Lebrech and his colleagues first introduced the use of non-selective beta-blockers (NSBB) for secondary prophylaxis of variceal bleeding in 1981^[8]. Then, Pascal and his colleagues expanded the role of NSBB to cover the primary prevention of variceal bleeding in patients with large esophageal varices^[9]. The use of propranolol not only showed a decreased rate of first bleeding in these patients, but it also demonstrated a survival benefit at 2 years^[9].

In spite of the proven clinical usefulness of beta-blocker therapy, its success is restricted by potential side effects and suboptimal treatment adherence. For example, studies in cardiology showed that the adherence to beta-blockers following a myocardial infarction declined with time^[19]. Also, some studies in hepatology showed that as few as 6 to 22% of patients with known medium to large varices received primary prophylaxis with NSBB^[20]. Moreover, beta-blockers have a lot of serious adverse effects such as heart failure exacerbation^[21], symptomatic bradycardia and high-grade AV block^[22], increased airways resistance^[23], peripheral artery disease exacerbation^[24], in addition to fatigue, depression, and sexual dysfunction^[25] among others.

Recently, it was suggested by some studies that beta-blockers may be effective only within a specific clinical window of advanced liver disease^[26]. Outside of this window, beta-blockers may be useless or even harmful (Table 2). For instance, in early cirrhosis, there is only mild splanchnic and systemic hyperdynamic circulatory

Table 1 List of studies showing benefits when beta-blockade therapy is used in liver cirrhosis.

Author	Year	Type of Trial	Results	P value	Mortality	P value
Lebrech <i>et al</i>	1981	Propranolol vs. Placebo for secondary prevention of variceal bleeding	Free of recurrent GI bleeding 96 vs. 50%	< 0.0001	Not studied	
Pascal <i>et al</i>	1987	Propranolol vs. Placebo for primary prevention of variceal bleeding	Free of first variceal bleeding 74 vs. 39%	< 0.05	Two year survival 72 vs. 51%	< 0.05
Lebrech <i>et al</i>	1988	Nadolol vs. Placebo for primary prevention of variceal bleeding	Free of first variceal bleeding 97 vs. 77%, only statistically significant in subgroup of compliant patients	< 0.02	Not studied	
Ideo <i>et al</i>	1988	Nadolol vs. Placebo for primary prevention of variceal bleeding	Free of first variceal bleeding 94 vs. 70%	< 0.02	No significant difference	
Italian multicenter project	1989	Propranolol vs. Placebo for primary prevention of variceal bleeding	Free of first variceal bleeding 74 vs. 59%. In subset of patients without ascites, free of first variceal bleeding in 83 vs. 61%	n.s. 0.028	42 month survival 51 vs. 59%	n.s.
					42 month survival 65 vs. 66%	n.s.

state, therefore NSBB are weakly active with some increase in their adverse events as it was shown in the large multicenter clinical trial from Groszmann and colleagues^[27]. On the other side, several circulatory changes accompany advanced cirrhosis such as peripheral vasodilation, effective hypovolemia, and arterial hypotension^[28-31], it is at that time when the maintenance of cardiac output and blood pressure becomes paramount in prolonging overall survival, and the hemodynamic effects of beta-blockers become potentially harmful^[26,32,33].

BLOOD PRESSURE AND CIRRHOSIS

In 1988, Llach and his colleagues studied the correlation between blood pressure and survival in patients with cirrhosis^[34]. They found that a mean arterial pressure (MAP) of ≤ 82 mmHg was an independent factor, most strongly correlated with reduced survival^[34]. For instance, 80% of patients with MAP ≤ 82 mmHg died at 24 months, and none of them survived at 48 months, in contrast with 30% of mortality rate at 24 months and 50% at 48 months among patients with MAP > 82 mmHg^[34]. Similarly, Krag and colleagues found that patients with a low cardiac index (< 1.5 L/min/m²) significantly developed more hepatorenal syndrome and had decreased survival rate compared to those with a cardiac index above 1.5 L/min/m²^[33]. Correspondingly, several studies confirmed this concept by showing that midodrine, an alpha-1 adrenergic agonist, was beneficial in patients with advanced cirrhosis^[35-39]. Midodrine therapy increased urinary volume, urinary sodium excretion, blood pressure, and decreased plasma renin activity and overall mortality^[39]. Also, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) reduced cardiac index and MAP resulting in worsened outcomes in patients with advanced cirrhosis and ascites^[40-43]. Finally, other studies of newer-generation beta-blockers such as carvedilol showed that although carvedilol may be more potent than propranolol in terms of reducing portal hypertension, it was associated with more systemic hypotension, increase in plasma volume and body weight, and worsening of pre-existing ascites^[44-47].

BETA-BLOCKERS IN DECOMPENSATED CIRRHOSIS AND REFRACTORY ASCITES

After almost three decades of their landmark study in 1981 showing the benefits of NSBB in the prevention of variceal bleeding in patients with cirrhosis^[8], the use of beta-blockers was questioned by Serste *et al* when they found out that NSBB therapy in patients with refractory ascites was associated with poor survival^[32]. In

their study, 151 patients with cirrhosis and refractory ascites were observed: Patients who were not treated with propranolol had a median survival of 20 months with a 64% probability of survival at 1 year whereas patients who were on propranolol therapy had a dramatically decreased median survival (5 months) with 19% probability of survival at 1 year only^[32]. In a subsequent study, Serste and colleagues showed that patients with advanced cirrhosis and refractory ascites who underwent regular large-volume paracentesis had a significantly higher risk of developing paracentesis-induced circulatory dysfunction if they were on NSBB therapy^[48]. This condition was associated with shortened survival even though it may be clinically silent^[49]. In addition, Mandorfer *et al* noticed an increased risk for hepatorenal syndrome and death in patients with cirrhosis and spontaneous bacterial peritonitis^[18]. These findings led to a reconsideration of beta-blocking therapy in cirrhotic patients especially those with advanced disease and refractory ascites.

Nevertheless, further studies showed inconsistent results in this matter. Some of them revealed that NSBB have a neutral effect on survival in patients with refractory ascites. For example, a study conducted by Galbois *et al* showed that patients with cirrhosis who were admitted to the hospital with sepsis had same survival rates regardless of NSBB therapy^[50]. Also, another study conducted by Robbins and his colleagues showed that patients with cirrhosis and refractory ascites undergoing regular paracentesis had same survival rate whether they were receiving a modest dose of propranolol or not^[51]. Moreover, other studies showed that NSBB may be beneficial in this category of patients. For instance, Mookerjee and colleagues noticed that treatment with NSBB was associated with reduced systemic inflammation and improved survival in patients with acute-on-chronic liver failure^[52].

At present, due to the paucity of available studies and their conflicting results, we lack sufficient evidence to draw definitive conclusions, especially that all of these studies are small, heterogeneous, and retrospective in nature, with variance in the definition of refractory ascites and lack of specific details about the enrolled patients such as the percentage of patients with refractory ascites, the percentage of patients with previous variceal bleeding, and the degree of hemodynamic disturbances (serum sodium level, MAP, etc.), among others.

RECOMMENDATIONS AND CONCLUSIONS

In this last part of the article, we are going to answer the most crucial questions concerning beta-blockade therapy and cirrhosis. And until solid evidences are available, the Baveno VI Consensus Workshop remains an important reference that physicians should rely on:

Table 2 List of studies showing harm when beta-blockade therapy is used in liver cirrhosis.

Author	Year	Type of Trial	Major Findings
Groszmann <i>et al</i>	2005	Timolol vs Placebo for prevention of gastrointestinal varices	No statistically significant difference in development of gastrointestinal varices. Adverse events 18% in timolol group vs 6% in placebo group ($p = 0.006$)
Krag <i>et al</i>	2010	CI and MAP in cirrhosis and ascites	6 month survival 50% and 1 year survival $< 40\%$ when CI < 1.5 L/min/ m ² 6 month survival $> 90\%$ and 1 year survival $> 70\%$ when CI > 1.5 L/min/ m ² 6 month survival 60% and 1 year survival $< 40\%$ when MAP ≤ 80 mmHg 6 month survival $> 80\%$ and 1 year survival $> 70\%$ when MAP > 80 mmHg
Serste <i>et al</i>	2010	Propranolol in patients with cirrhosis and refractory ascites	1 year survival 19% in patients treated with propranolol, 1 year survival 64% in patients not treated with propranolol ($p < 0.0001$)
Serste <i>et al</i>	2011	Propranolol and development of paracentesis-induced circulatory dysfunction	Significant decrease in MAP after paracentesis with development of paracentesis-induced circulatory dysfunction among patients given propranolol, decreased development of paracentesis-induced circulatory dysfunction after discontinuation of propranolol

CI: Cardiac Index; MAP: Mean Arterial Pressure

When to use beta-blockers in cirrhosis

At this time, there is still no indication to use beta-blockers to prevent the formation of varices or to prevent bleeding in patients with small varices without signs of increased risk (1b;A)^[53]. On the other hand, patients who have small varices with red wale marks or Child-Pugh C class have an increased risk of bleeding and should be treated with NSBB (1b;A)^[53]. Likewise, patients with medium to large varices that haven't bled yet should receive either NSBB therapy or endoscopic variceal ligation (EVL) as primary prophylaxis (1a;A)^[53]. Finally, in order to prevent recurrent variceal hemorrhage, the first line therapy recommended for all patients is the combination of NSBB along with EVL (1a;A)^[53]. Monotherapy should not be used unless there is contraindication/intolerance to NSBB or inability or unwillingness to be treated by EVL (1a;A)^[53].

Which beta-blocker to prescribe

Traditional NSBB (propranolol, nadolol) (1a;A) and newer-generation beta-blockers (carvedilol) (1b;A) are effective first-line therapy for primary prevention of variceal bleedin^[53]. Carvedilol was found to be more effective than traditional NSBB in reducing hepatic venous pressure gradient (HVPG) (1a;A) but hasn't been sufficiently compared head-to-head to the standard of care therapy in clinical trials^[53]. However, only traditional NSBB (propranolol, nadolol) are indicated for secondary prevention of variceal bleeding (1a;A)^[53]. The use of carvedilol cannot be recommended in the prevention of rebleeding due to lack of evidences^[53].

Use of NSBB in patients with end-stage liver disease

Recently, patients with end-stage liver disease and refractory ascites became a subgroup of interest because the safety of NSBB in this specific group has been questioned (2b;B)^[53]. But no firm contraindications have been recommended. The use of NSBB in this class of patients may still play a role, however great caution should be taken and close monitoring of the patients is recommended and a reduction of the dose or discontinuation of the treatment may be considered if acute kidney injury ensues, systolic arterial pressure drops below 90mmHg, or hyponatremia below 130 mEq/L occurs^[53]. When beta-blockade therapy is stopped, endoscopic band ligation

becomes highly recommended^[53].

In conclusion, many questions remain with regards to the exact therapeutic parameters of beta-blockers in patients with cirrhosis in general, and in patients with refractory ascites in particular, and additional studies on the optimal timing and dosage of beta-blockers are certainly needed. Perhaps the most appropriate timing for beta-blocker therapy was outlined in the "window hypothesis" from Krag and colleagues which suggests that beta-blockers are beneficial only in a narrow clinical window in the course of cirrhosis^[26]. This dilemma will be resolved only by a prospective randomized controlled trial, but until that evidence becomes available, the Baveno VI Consensus Workshop (table 3) provides practical clues to guide physicians' decision about NSBB therapy in patients with decompensated cirrhosis.

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Table 3 Summary of recommendations for beta-blockade therapy in patients with liver cirrhosis according to the BAVENO VI consensus workshop.

Clinical situation	Recommendation for beta-blockers
Early cirrhosis	
Without medium to large esophageal varices	Not indicated for cirrhosis, however may be indicated for concurrent cardiovascular disease
Compensated cirrhosis	
With medium to large esophageal varices	Indicated to prevent first episode of variceal bleeding. Caution should be taken to avoid systemic hypotension
Decompensated cirrhosis	
Initial episode of variceal bleeding	Indicated to prevent recurrent variceal bleeding. Caution should be taken to avoid systemic hypotension
With sepsis or hepatorenal syndrome	Discontinue existing beta-blockers
End-stage cirrhosis	
With refractory ascites	Not indicated due to decreased cardiac output and risk for hypotension and renal failure. Existing beta-blockers should be tapered and then discontinued. Consider alternative treatment modality such as endoscopic band ligation. Consider midodrine to increase blood pressure
Other clinical scenarios	
Patients with poor compliance or inadequate follow-up care	Not indicated as risks of causing harm may substantially outweigh potential benefits
Routine office visit for patient with good compliance	Adjust beta-blockers based on serial blood pressure measurements over time. Titrate to 25% reduction in baseline heart rate, or goal heart rate 55 beats/minute, as blood pressure and side effects tolerate. Home monitoring of pulse and blood pressure is superior to a single clinic measurement

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