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The changing role of beta-blocker therapy in patients with cirrhosis

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Summary

Cirrhosis is a leading cause of death in the United States and worldwide. Beta-blockers have been established in numerous studies as part of the cornerstone of the medical management of cirrhosis, particularly in the primary and secondary prevention of variceal hemorrhage. However, new evidence has cautioned the use of beta-blockers in patients with end-stage cirrhosis and refractory ascites. In this article, we review the beneficial effects of beta-blocker therapy, the potential harms of aggressive beta-blocker therapy, and provide suggestions regarding the appropriate use of this class of medications in patients with cirrhosis.

Introduction

Cirrhosis is a leading cause of mortality in the United States and worldwide [1,2]. Within the developed world, the leading causes of cirrhosis include alcoholic liver disease, hepatitis C, and more recently, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). Ever since NASH was described as a cause for cryptogenic cirrhosis [3], there has been increasing recognition that NASH may become the most common cause of advanced liver disease in the coming decades [4]. It is projected that between 2015 and 2030, NASH cirrhosis will overtake hepatitis C cirrhosis as the most common indication for liver transplantation in the United States [5]. Studies have also implicated NASH risk factors including metabolic disease as being co-morbid with chronic hepatitis C [6] and alcoholic liver disease [7]. Some patients have all three insults to their liver.

Given the comorbidity of hypertension, metabolic syndrome, and NASH cirrhosis, increasing numbers of patients with chronic liver disease are now on antihypertensives for essential hypertension. In a study of outpatient antihypertensive prescribing behavior, ambulatory visits by adults having uncomplicated essential hypertension increased 33% from 29.8 million visits in 1993 to 39.6 million visits in 2004 [8]. Beta-adrenergic antagonists ("beta-blockers") have been established as part of the cornerstone of the medical management of hypertension [9], as well as acute coronary syndrome [10], and congestive heart failure [11].

Beta-blockers have also been well established in the prevention of variceal hemorrhage in patients with cirrhosis [12–15]. The use of non-selective beta-blocker therapy in the secondary prevention of variceal hemorrhage was first introduced in 1981 [12]. Subsequent studies expanded the role of non-selective beta-blockers to include primary prevention of variceal hemorrhage in patients with known cirrhosis and large esophageal varices [13]. Beta-blocker therapy has been demonstrated to be cost-effective [16–18], and may be also beneficial in the prevention of other complications of cirrhosis and portal hypertension, including bleeding from portal hypertensive gastropathy [19,20], and the development of spontaneous bacterial peritonitis [21]. However, new studies have cautioned the use of beta-blockers in patients with decompensated cirrhosis [22,23]. Updated recommendations are therefore needed regarding the appropriate use of beta-blockers in patients with cirrhosis.

Beta-blockers in cirrhosis

In its early stages, liver disease is often asymptomatic. As cirrhosis advances, portal hypertension develops, resulting in ascites, hepatic encephalopathy, and variceal hemorrhage. Ascites is the most common major complication of cirrhosis, occurring in 50% of patients within ten years of diagnosis [24]. The presence of ascites is an ominous landmark in the progression of cirrhosis, as 15% of patients with ascites will succumb within 1 year, and 44% within 5 years [25]. Over one third of patients diagnosed with cirrhosis develop esophageal varices within three years of diagnosis [26].

Circulatory disturbances also develop, including increased cardiac output and heart rate, decreased systemic vascular resistance, and decreased mean arterial blood pressure. The most widely accepted explanation of the hemodynamics in cirrhosis, the peripheral arterial vasodilatation hypothesis [27], states that systemic vasodilatation from reduced systemic vascular resistance leads to arterial underfilling, which together with the sequestration of fluid into the peritoneal cavity, activates

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salt-retaining mechanisms and neurohormonal systems such as the sympathetic nervous system and the renin-angiotensin-aldosterone system to counteract low arterial blood pressures [28]. As a result, although plasma and blood volume is increased in cirrhosis, patients with decompensated cirrhosis and ascites have a decreased effective arterial blood volume [27–30]. Paracentesis further induces arteriolar vasodilation and results in additional decrease in effective arterial blood volume [31].

It is in this pathophysiological context that beta-adrenergic blockade has both theoretical benefits as well as adverse effects. Non-selective beta-blockers such as propranolol and nadolol achieve their effects through the dual mechanism of reducing cardiac output via beta-1 adrenergic blockade, and reducing portal blood flow through splanchnic vasoconstriction via beta-2 adrenergic blockade [32]. Both mechanisms are clearly necessary for these medications to be safe and effective in cirrhosis; selective beta-1 antagonists such as metoprolol and atenolol have been shown to be less effective and are not recommended for the prophylaxis of variceal hemorrhage [33,34].

Benefits of beta-blocker therapy

The use of non-selective beta-blocker therapy was first introduced by Lebrec and colleagues in 1981 [12]. In their study, 74 patients presenting with a first episode of variceal bleeding were randomized to either placebo or oral propranolol targeted to a 25% reduction in heart rate. They found that 96% of patients in the propranolol group were free of recurrent gastrointestinal bleeding at one year, compared to 50% of patients in the placebo group [12]. The findings from this and additional studies established the role of non-selective beta-blockers in the secondary prevention of gastrointestinal hemorrhage [35].

Subsequent studies expanded the role of non-selective beta-blockers. Pascal and colleagues in 1987 studied the role of propranolol in the prevention of a first upper gastrointestinal bleeding event in patients with known cirrhosis [13]. In their study, 230 patients with large esophageal varices without previous episodes of bleeding were randomized to either placebo or propranolol targeted to a 20–25% reduction in heart rate. They found that 74% of patients in the propranolol were free of variceal bleeding at one year, compared to 39% in the placebo group, suggesting that propranolol has a role in decreasing the incidence of the first episode of upper gastrointestinal bleeding in patients with cirrhosis [13]. Similarly, two year survival was 72% in the propranolol group, compared to 51% in the placebo group, demonstrating a significant survival benefit in the use of propranolol in patients with cirrhosis and large esophageal varices [13]. A meta-analysis from Poynard and colleagues in 1991 analyzed four randomized clinical trials [13,36–38], and determined that non-selective beta-blockers are effective in preventing first bleeding episode and reducing the mortality rate from gastrointestinal bleeding among patients with cirrhosis [14]. Additional meta-analyses have since established the use of non-selective beta-blockers as first-line pharmacotherapy in both primary and secondary prevention of variceal hemorrhage (Table 1) [15,39].

Adverse effects of beta-blocker therapy

Despite the proven clinical effectiveness of beta-blocker therapy, its success is limited by potential adverse effects and suboptimal treatment adherence. Studies in the cardiology literature have shown that patient adherence to beta-blocker therapy following myocardial infarction decline substantially over time [40]. Similarly, studies in the hepatology literature have suggested that despite well established guidelines and recommendations, as few as 6–22% of patients with known medium or large varices received primary prophylaxis with beta-blockers [41]. Side effects led to treatment discontinuation in approximately 15% of patients in the various beta-blocker trials in patients with cirrhosis [32].

Beta-blocker therapy can result in both cardiac as well as non-cardiac adverse effects. The decrease in cardiac output from beta-1 antagonism may cause major cardiac side effects. Despite the central role of beta-blockers in the management of congestive heart failure, beta-blockers may also exacerbate heart failure, or even precipitate heart failure in patients with pre-existing cardiac dysfunction and borderline compensation who are reliant upon sympathetic drive [42]. Beta-blockers also significantly decrease chronotropy, depressing conduction through the atrioventricular node. This can result in symptomatic bradycardia, or even high grade heart block [43].

The acute withdrawal of beta-blocker therapy can lead to serious morbidity and potential mortality [44]. Abrupt cessation of beta-blocker therapy can result in accelerated angina, myocardial infarction, and sudden death, even in patients who do not previously have coronary artery disease [45,46]. These symptoms are presumably due to rebound sympathetic activity resulting in a hyperadrenergic state, which is more likely to occur with shorter-acting medications such as propranolol [47].

Most of the major non-cardiac adverse effects of beta-blockers result from the non-selective beta-adrenergic blockade. Non-selective beta-blockers can result in increased airways resistance in patients with bronchospasm, and therefore should be avoided in patients with known bronchospastic diseases [48]. Nonselective beta-blockers can also cause exacerbations of peripheral artery disease due to the reduction of cardiac output and blockade of beta-2-adrenergic skeletal muscle vasodilation, resulting in local vascular insufficiency. Initial studies of patients with peripheral artery disease taking propranolol showed complications of claudication, cold extremities, absent pulses, cyanosis, and impending gangrene [49]. Additionally, in patients with diabetes mellitus, glucose recovery from insulin-induced hypoglycemia is dependent on epinephrine-mediated beta-adrenergic mechanisms, which can be dangerously impaired by the use of non-selective beta-blockers such as propranolol [50]. Finally, commonly reported side effects from beta-blockers also include depression, fatigue, and sexual dysfunction [51]. It has been previously hypothesized that these symptoms are associated with central nervous system effects of older generation lipophilic beta-blockers such as propranolol, however a meta-analysis of clinical trials showed no increased risk of depression and small increases in fatigue and sexual dysfunction, without significant differences by the degree of beta-blocker lipid solubility [52].

Studies of beta-blockers in the cardiology literature have almost uniformly suggested that side effects are decreased with selective beta-1 antagonists. However, selective beta-1 antagonists such as metoprolol and atenolol have been shown to be less effective in portal hypertension and are not recommended for the prophylaxis of variceal hemorrhage [33,34]. Additional studies focused on adverse effects of non-selective beta-blockers have been generally lacking. It should be noted that adverse effects