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Safety of betablockers for prophylaxis of portal hypertension in different child pugh classes of chronic liver disease - a review

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ABSTRACT

Portal hypertension, one of the main complications of cirrhosis is a pathological increase of the portal pressure gradient and by the formation of portal-systemic collaterals that shunt part of the portal blood flow to the systemic circulation bypassing the liver. Non-selective beta-blockers (NSBBs) have been used for over 30 years for the primary and secondary prophylaxis of portal hypertension in patients with cirrhosis. NSBB decreases cardiac output via β1 receptors and causes splanchnic vasoconstriction through β2 receptors, leading to a reduction in portal inflow. They have proven efficacy in preventing first variceal bleeding and re-bleeding and in reducing mortality. The advantage of using NSBBs must be weighed against the risks associated with their chronic use. In addition recent data suggest about the limited use of NSBBs in a particular therapeutic window only. Outside this window it may cause deleterious effects. The beneficial window of NSBBs opened by the first appearance of esophageal varices at the risk of bleeding and would be closed by the development of refractory ascites or other severe complications like spontaneous bacterial peritonitis(SBP) / hepatic renal syndrome (HRS) the clinical hall mark of advanced liver diseases. The risk/benefit ratio of the non selective beta blocker therapy depends up on the stages of the cirrhosis, perhaps becoming unfavourable in patients with the most advanced stage. This article reviews the current evidence regarding the safety of non selective beta blockers in different Child Pugh classes of chronic liver disease for portal hypertension prophylaxis.

INTRODUCTION

Cirrhosis and chronic liver failure are the leading causes of morbidity and mortality with majority of preventable cases attributed to excessive alcohol consumption, viral hepatitis, or non alcoholic fatty liver disease. Most of the patients remain asymptomatic until the occurrence of decompensation , characterised by ascites, spontaneous bacterial peritonitis, hepatic encephalopathy or variceal bleeding from portal hypertension.[1]

The severity of cirrhosis is important to assess because it serves as a predictor of patients survival, surgical outcomes and the risk of complications such as variceal bleeding. Assessment tool commonly used in cirrhosis patient includes Model for End stage liver disease (MELD), which has score ranging from 0-40, and the Child Pugh classification system which has a score ranging from 0-15. Patients with higher MELD score have a poor prognosis than patients with a lower score .The Child Pugh score is used to group the patients into three categories 1) Class A score of less than 7 (Mild disease) 2) Class B score of 7-9(moderate disease), Class C score of 10-15 (severe disease).Cirrhosis patients who do not receive a liver transplant have a 5year mortality rate of up to 85%. [2] Portal hypertension, one of the main complication of cirrhosis is hemodynamically defined by a pathological increase of the portal pressure gradient (the pressure difference between the portal vein and the inferior vena cava) and by the formation of portal-systemic collaterals that shunt part of the portal blood flow to the systemic circulation bypassing the liver. Normal values of the portal pressure gradient are of 1-5 mm Hg. [3] When the Hepatic venous pressure gradient (HVPG) increases to 10 mmHg or more then the cirrhotic patient is at risk of decompensation. Thus, an HVPG ≥10 mmHg defines the

presence of clinically significant portal hypertension (CSPH). Values of portal pressure gradient between 5 and 9 mm Hg correspond to pre-clinical portal hypertension.[4]

Portal hypertension that result from the chronic liver disease can cause further complications including the development and bleeding of varices.[2] Around 50% of patients with cirrhosis develop gastroesophageal varices , and their presence correlates with the severity of liver disease.[5] The strongest predictor of the occurance of varices in cirrhosis patients without a history of variceal bleeding is a HVPG of greater than 10mm Hg.[6] [2]The risk factor associated with the progression of varices (eg: small to large varices) includes decompensated cirrhosis(Child Pugh Class B and C),alcoholic cirrhosis and presence of red wale marks on the baseline endoscopy.[6][7]Gastroesophageal varices can progress to variceal bleeding with HVPG of 12 mmHg. Strong predictors for variceal bleeding include varix size (highest risk of bleeding with large varices, greater than 5mm),severe liver disease(Child Pugh Class C cirrhosis),presence of ascites or tense ascites and previous variceal bleeding .[8]

Because of the high mortality and morbidity of variceal bleeding, primary prevention of bleeding is a major goal in the management of portal hypertension, which in turn depends on the phase of portal hypertension at which the patient is situated.[7] The prevention of variceal bleeding is categorised into primary and secondary prophylaxis. The goals of primary prophylaxis are to detect the presence and size of the varices and to prevent the first variceal haemorrhage. The goal of secondary prophylaxis is to prevent the variceal bleeding recurrence.[2] For primary prophylaxis patients are classified as having highest risk of variceal bleeding when they are presented with medium/large varix ,red wale marks on varix and Child Pugh class C . Patients with lowest risk of variceal bleeding include those with no varices;it is not recommended to give beta blockers prophylaxis.[2] In primary prophylaxis, patients with high risk small varices or large/medium varices should receive primary prophylaxis either with NSBB or with endoscopic band ligation if they are contraindicated to NSBB. For secondary prophylaxis the current recommendation is to receive a combination of NSBB and endoscopic variceal ligation.[9]

Non selective betablockers are more effective than selective beta blockers in preventing variceal bleeding because of their beta1 and beta2 antagonistic properties. NSBB decreases cardiac output via β1 receptors and causes splanchnic vasoconstriction through β2 receptors, leading to a reduction in portal inflow. [9] Propranolol and nadalol with beta 1 and beta 2 antagonistic properties were the most commonly used NSBB for the prophylaxis of variceal bleeding. Carvedilol is NSBB with intrinsic alfa 1 adrenergic activity has a potent hypotensive effect which is superior to propranolol. But Carvedilol has a greater potential to cause systemic hypotension especially in patients with cirrhosis and ascites.[10]

In fact, NSBBs have become one of the most effective preventive therapy in patients with cirrhosis against variceal bleeding.[4] The advantage of using NSBBs must be weighed against the risks associated with their chronic use.[11] NSBBs are contraindicated in patients with refractory asthma, severe COPD , advanced atrio-ventricular block, and severe arterial hypotension. The adverse effects associated with NSBBs such as bronchospasm, hypotension, light-headedness, fatigue, impotence and sleep disorders requires early recognition and monitoring.[12] NSBB can be started only to the patient that can be properly followed in terms of blood pressure and frequent blood test (at least weekly during titration). Discontinuation of the therapy is needed if systolic blood pressure decreases below 95 mmHg, if the patient experiences orthostatic symptoms, or if there is an increase in creatinine that appears attributable to NSBB therapy. Septic episodes also requires discontinuation of NSBBs. [4]

Non selective beta-blockers may be effective only within a particular clinical window of advanced liver disease. Outside of this window, beta-blockers may be ineffective in early cirrhosis with some increased adverse events, and potentially harmful in advanced cirrhosis.[13]

In early cirrhosis, beta-blockers did not show any effect on survival because it increases the adverse events and do not prevent the formation of varices.[13][9] So the initiation of beta-blockers is not recommended in the early stage for the purpose of preventing gastrointestinal bleeding, although they may be indicated for cardiac co morbidities such as coronary artery disease and congestive heart failure.

During the progression of the disease, portal pressures increases and the sympathetic nervous system becomes increasingly activated, medium to large esophageal varices develop, and there is increased risk of variceal bleeding and bacterial translocation from the gut. Ascites also develop at this stage. From a cardiovascular perspective, systemic hemodynamics is still relatively preserved, cardiovascular reserve is intact, and blood pressure and cardiac output are maintained to deliver adequate end-organ perfusion. In this middle stage of cirrhosis, beta-blockers have been shown in numerous trials to have survival benefit. [14]

The NSBBs usage in the middle stage of the cirrhosis causes a reduction in the development of ascites ,refractory ascites and hepato renal syndrome. In addition NSBB treatment has been shown to decrease intestinal permeability independently of hemodynamic response and to prevent the development of SBP.[15]

In advanced cirrhosis, various circulatory changes occur, including the up-regulation of the sympathetic nervous system and renin-angiotensin-aldosterone system. These circulatory changes, along with the development of sodium and water retention and the formation of ascites, are aimed at maintaining adequate cardiac output and organ perfusion. They reflect an adaptive response to the peripheral vasodilation, effective hypovolemia, and arterial hypotension which accompanies advanced cirrhosis. When the cirrhosis progresses, the cardiovascular system eventually loses its compensatory ability. In this stage the maintenance of blood pressure and cardiac output is paramount in prolonging overall survival, and there is evidence that the hemodynamic effects of beta-blockers in reducing blood pressure and cardiac output may result in decreased survival in this patients. So in this final stage of cirrhosis NSBB neither be recommended nor be initiated.[13]

The beneficial window of NSBBs opened by the first appearance of esophageal varices at the risk of bleeding and would be closed by the development of refractory ascites , or other complications like SBP/HRS that are clinical hall mark of advanced liver diseases.[16] In advanced stage of cirrhosis, generally reflected by refractory ascites, there is an emerging evidence that the use of beta-blockers reduce survival. Patients with cirrhosis and refractory ascites are characterized by low

systemic blood pressure and reduced renal perfusion with low glomerular filtration progressing to type 2 hepatorenal syndrome (HRS). Such patients are also susceptible to complications such as sepsis including SBP, hepatic encephalopathy, and type 1 HRS. Therefore the use NSBB which has a hypotensive effect could be detrimental for patients with refractory ascites. Administration of NSBB in this case may contribute to the development of post paracentesis-induced circulatory dysfunction, a syndrome contributed to a increased mortality among patients with cirrhosis and tense ascites.[11][17]

Development of SBP in the cirrhosis also closes the window of opportunity for the NSBB treatment, as maintenance of the circulatory reserve is crucial in critically ill patients with cirrhosis. The main adaptive response to the circulatory stress is the increase heart rate mediated by beta 1 adrenoreceptors that are downregulated and desensitised in advanced cirrhosis patients. Additional blockade by the NSBBs induces chronotropic incompetence, decrease cardiac output and blood pressure and increases the rate of development of HRS after an SBP episode, results in worsening of survival.[15]

The use of NSBB on "cirrhotic cardiomyopathy", which is common but often underdiagnosed in patients with advanced cirrhosis also creates a potentially negative effect. Cirrhotic cardiomyopathy is a newly recognized condition characterized by diastolic dysfunction, systolic incompetence under conditions of stress, and electrophysiological abnormalities. Some characteristics of cirrhotic cardiomyopathy, such as diastolic dysfunction, reduced cardiac index, and Q-T interval prolongation, have been significantly associated with complications of cirrhosis, such as HRS, and death. Therefore, if the use of NSBBs further impair cardiac function in a patient with cirrhotic cardiomyopathy, this could be another mechanism whereby NSBBs administration would lead to an unfavorable outcome.[11]

CONCLUSION

NSBBs can be used safely in cirrhosis patients within a particular clinical window. Outside this window it may cause deleterious effects. The beneficial window of NSBBs opened by the first appearance of esophageal varices at the risk of bleeding and would be closed by the development of refractory ascites or other severe complications like spontaneous bacterial peritonitis(SBP) / Hepatic renal syndrome (HRS) the clinical hall mark of advanced liver diseases .The risk/benefit ratio of the therapy varies according to the stage of the cirrhosis, perhaps becoming unfavorable in patients with the most advanced stage.

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