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Beneficial and Harmful Effects of Non-selective Beta Blockade on Acute Kidney Injury in Liver Transplant Candidates

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Abstract

Non-selective beta-blockers have played an important role in the prevention of portal hypertensive bleeding in cirrhotic patients. However, recent studies have suggested that non-selective beta-blockers may be harmful in some patients with end-stage liver disease. To evaluate the association between use of non-selective beta-blocker and the incidence of acute kidney injury (AKI). We conducted a nested case-control study in a cohort of liver transplant waitlist registrants. Each patient with AKI was matched to a control by the model for end-stage liver disease (MELD)-Na score, age, serum creatinine, and follow-up duration. Out of a total of 2,361 waitlist registrants, 205 patients developed AKI after a median follow-up duration of 18.2 months. When compared to matched controls, ascites (79.0% versus 51.7%) and non-Caucasian race (16.6% versus 7.8%) were more common among the cases. The frequency of non-selective beta-blocker use was higher among the cases than controls, albeit insignificantly (45.9% versus 37.1%, $P = .08$). In multivariable analyses, the impact of non-selective beta-blockade on the development of AKI was dependent upon the presence of ascites: non-selective beta-blockade in patients with ascites significantly increased the risk of AKI (hazard ratio [HR], 3.31; 95% confidence interval [CI], 1.57-6.95), while in patients without ascites, non-selective beta-blocker use reduced it (HR, 0.19; 95% CI, 0.06-0.60). Potential benefits and harms of a non-selective beta-blocker in terms of AKI depend on the presence of ascites in liver transplant candidates. Non-selective beta-blocker therapy in cirrhotic patients may need to be individualized.

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Keywords

Adrenergic Beta-Antagonists; Acute Kidney Injury; Liver Cirrhosis

Introduction

Non-selective beta-blockers have been widely used in patients with cirrhosis with gastroesophageal varices.¹ A number of randomized clinical trials have shown the efficacy of non-selective beta-blockers in primary and secondary prevention of variceal hemorrhage.²⁻⁶ Non-selective beta-blockers have been associated with improved survival, particularly when their use results in satisfactory reduction in the hepatic vein portal pressure gradient (HVPG).⁷⁻¹⁰

In patients with cirrhosis, development of renal dysfunction represents an important landmark in their disease progression. For example, hepatorenal syndrome (HRS), particularly of type 1, is a serious complication with a high risk of mortality. HRS is thought to result from the pervasive hemodynamic changes that occur in patients with cirrhotic portal hypertension, including splanchnic vasodilation and hypoperfusion of renal vasculature. More recently, standardized definitions of acute kidney injury (AKI) have been increasingly applied in cirrhotic patients with evidence of decreased renal function.¹¹ Worsening stages of AKI in patients with cirrhosis are associated with a progressive increase in mortality risk.¹²

The effect of non-selective beta-blockade on development of renal dysfunction in patients with cirrhosis is uncertain. Earlier studies, which mainly included patients with compensated cirrhosis, reported that the hemodynamic response to a non-selective beta-blocker is associated with reduced risk of developing ascites, refractory ascites, and HRS.² More recently, in patients who have had spontaneous bacterial peritonitis (SBP) and end-stage liver disease, non-selective beta-blocker use was associated with higher incidence of HRS and AKI.^{13,14} One potential explanation for these contradictory observations may be that the effects of non-selective beta-blockers on the kidney may be dependent upon the severity of hepatic decompensation - there is a finite time 'window' in which non-selective beta-blockers are clinically beneficial.¹⁵

In this work, we hypothesized that the hemodynamic effects of non-selective beta-blockers, including reduced arterial blood pressure and cardiac output, may increase the risk of renal hypoperfusion and AKI in susceptible patients with cirrhosis. Our primary aim was to examine whether long-term use of a non-selective beta-blocker is associated with development of AKI in cirrhotic patients waitlisted for liver transplantation. Specifically, we compare the use of non-selective beta-blockers between cirrhotic patients who develop AKI and those who did not. Secondly, we determine risk factors that contribute to the occurrence of AKI. In particular, we look for evidence in support that renal effects of non-selective beta-blockers may be dependent upon the severity of hepatic decompensation.

Patients and Methods

Study Design / Subjects

This is a nested case-control study derived from a cohort of liver transplant candidates. The parent cohort consisted of all adult patients with liver cirrhosis who were waitlisted for liver transplantation at Mayo Clinic, Rochester between January 1990 and December 2010. The long period covered in this study was to maximize its statistical power, namely the number of patients developing AKI. While the outcome of patients with portal hypertension may have improved incrementally during the period, no substantial change in the medical management of patients with cirrhosis occurred to the extent to have altered the biological relationship between beta blockade and AKI. The study was approved by the Institutional Review Board of the Mayo Foundation.

A nested case-control study design preserves advantages of a cohort study while avoiding potential biases of a conventional case-control study. Since the cases and controls come from the same population, causal relationship could be assessed appropriately between exposure (i.e., non-selective beta-blocker) and outcome (i.e., AKI). Each AKI case was individually matched to a control by a number of variables that may confound the incidence of AKI. They included age, serum creatinine and model for end-stage liver disease (MELD)-Na¹⁶ at baseline and follow-up duration. As exact matching in all of these variables was not feasible, an allowable window of tolerance was defined for each variable (see Table 1 footnote for details). Most of the data used in the study were extracted from an institutional transplant database which has been described previously.¹⁷ In both cases and controls, individual medical records were reviewed to obtain clinical details of non-selective beta-blocker use.

Cases were defined as patients developing de novo AKI stage 2 during the follow-up.^{18,19} In order for a patient to be designated to be a case, the following criteria had to be met: (1) waitlist registration for chronic liver disease with histological or clinical evidence of cirrhosis, (2) a minimum of one month of follow-up after liver transplantation waitlist registration, (3) available serum creatinine data at waitlist registration and (4) an increase of serum creatinine to more than 2 times the baseline value without a clear precipitating cause (e.g., radiocontrast induced nephrotoxicity). The urine output component of the AKI definition was not applied, because necessary data were not available. Patients with prior history of kidney or liver transplantation or abnormal renal function (serum creatinine > 1.5 mg/dL) or receiving hemodialysis at baseline were excluded. Patients with incomplete information about the use of non-selective beta-blockers were also excluded from the analysis. Patients were censored upon liver transplantation, death or at the end of follow-up in the absence of AKI. These events were verified with the information from the medical records and registration data.

Data Analysis

The goal of the analysis was to compare the proportions of patients receiving non-selective beta-blockers between cases and controls. Thus, the primary predictor variable in this study was the use of a non-selective beta-blocker. This was operationally defined as having received a non-selective beta-blocker both at baseline and on the day of occurrence of AKI

in cases and on the last day of observation in controls. This was because it is practically impossible to obtain an active medication list and ascertain its accuracy at all times in the medical record. Recent data reassure that short-term interruption of a non-selective beta-blocker does not affect clinical or hemodynamic status of a cirrhotic patient.²⁰ In examining the applicability of the 'window' concept, analyses were stratified by the presence of ascites detected by imaging (e.g., ultrasonography or computed tomography) or by the use of diuretics with history of ascites.

In comparing cases and controls, the proportional hazards regression analysis was performed to identify predictors of AKI. Given the study design, all analyses were undertaken stratifying on the matches. Unadjusted Cox models were created for demographic (age, sex, and race), major clinical variables (liver cancer, diabetes, esophageal varices, ascites), and laboratory parameters (total bilirubin, international normalized ratio [INR], creatinine, sodium) as well as MELD-Na and non-selective beta-blocker use. Multivariable Cox regression was performed based on variables with un-adjusted *P* values < 0.1. In addition, variables used in matching, namely age, MELD-Na, and serum creatinine were included in order to control for any residual confounding. Adjusted Kaplan-Meier curves were created to compare the survival rates among subjects according to the ascites and non-selective beta-blocker status. Analyses were implemented using SAS (Version 9.3; SAS Institute Inc., Cary, NC) and R (version 3.0.2) statistical software packages.

Results

Patient Characteristics

Out of the cohort of 2,361 waitlist registrants, 252 patients developed AKI and 205 patients met the specified eligibility criteria. Fig. 1 represents a flow diagram illustrating the process by which cases and controls were selected.

Table 1 compares baseline characteristics of the cases and controls. The median follow-up duration was 18.2 months (range, 1-198.2 months). The most common etiology of liver cirrhosis was viral hepatitis (26.8%). The mean ($\pm$ standard deviation [SD]) age was 52.2 $\pm$ 9.6 years with a slight female preponderance (52.9%) and Caucasian majority (87.8%). According to the matching algorithm, 205 patients who did not meet the criteria for AKI were selected as controls. When compared to matched controls without AKI, ascites (79.0% versus 51.7%) and non-Caucasian race (16.6% versus 7.8%) were noticeably more common among the cases. However, no significant difference was found in age, sex, MELD score, diabetes mellitus, presence of esophageal varices between the two groups.

Use of Non-Selective Beta-Blockers in Cases and Controls

Cases and controls combined, a total of 170 patients received non-selective beta-blockers for the prevention of portal hypertensive bleeding. The initial non-selective beta-blocker prescribed was propranolol in 81 patients and nadolol in 89 patients. There were nine patients who were switched from one non-selective beta-blocker to another, including six patients switching from propranolol to nadolol. Overall, the frequency of non-selective beta-blocker use was higher, although non-significantly, among the cases than the controls

(45.9% versus 37.1%, respectively). The median dose of non-selective beta-blocker between the cases and controls was not different (propranolol equivalent 40.0 mg/dL [interquartile range (IQR), 30.0-60.0] versus 40.0 mg/dL [IQR, 40.0-60.0; $P = 0.12$]). However, the median duration of non-selective beta-blockers use was longer in the controls compared to the cases (27.0 months [IQR, 11.5-57.0] versus 12.0 months [IQR, 5.0-39.0], respectively, $P < 0.01$), reflecting the stability of the clinical course in the former.

Non-Selective Beta-Blocker Use and the Risk of Developing Aki

In the unadjusted proportional hazard regression analysis for predicting the development of AKI (Table 2), non-Caucasian of race, high MELD and MELD-Na scores at baseline, and presence of ascites were associated with an increased risk of AKI, whereas autoimmune etiology was associated with a decreased risk. In investigating whether the incidence of AKI differs between the cases and controls depending upon the presence of ascites, patients were divided into four groups, namely non-selective beta-blocker users and non-users with and without ascites, respectively. Fig. 2 shows that the incidence of AKI is higher, as expected, among the two groups of patients with ascites than in those without. More importantly, the effect of non-selective beta-blocker was in the opposite direction between patients with and without ascites. Among patients with ascites, non-selective beta-blocker users experienced higher incidence of AKI, whereas among those without ascites, the incidence of AKI was much lower in non-selective beta-blocker users, compared to those not taking a non-selective beta-blocker.

Table 3 formally examines the effect of non-selective beta-blocker and ascites on the risk of AKI with the multivariable Cox regression analysis. After adjusting for demographic variables, MELD-Na at baseline was associated with significantly increased hazards of developing AKI (hazard ratio [HR], 1.66; 95% confidence interval [CI], 1.36-2.03; $P < 0.01$). As suggested by Fig. 2, there was a significant interaction between non-selective beta-blocker and ascites: non-selective beta-blocker use in patients with ascites increased the risk of AKI by over 3 fold (HR, 3.31; 95% CI, 1.57-6.95; $P < 0.01$); whereas in patients without ascites, non-selective beta-blockade reduced the risk of AKI by approximately 5 fold (HR, 0.19; 95% CI 0.06-0.60; $P < 0.01$).

Discussion

The main finding in this study is that the effect of non-selective beta-blockers on the development of AKI in cirrhotic patients is bidirectional depending on the presence of ascites. In patients without ascites, non-selective beta-blocker use was associated with an 80% reduction in AKI, whereas once ascites is present, it increased the risk of AKI by more than three-fold. As expected, in addition to the use of a non-selective beta-blocker in the presence of ascites, increasing MELD-Na (or MELD) was associated with a higher incidence of AKI. Although cases and controls were matched by MELD-Na, the matching was incomplete and even within the relatively narrow range of MELD-Na scores (<7 points) allowed in matching, there still was a significant residual effect of MELD-Na on the development of AKI as reported in Table 3.

Non-selective beta-blockers are some of the most commonly prescribed drugs in patients with cirrhosis, as they represent a simple and relatively safe means to prevent portal hypertensive gastrointestinal bleeding. The current practice guidelines recommend early institution and indefinite continuation of non-selective beta-blockers to prevent gastroesophageal variceal bleeding.²¹ For example, emerging data have suggested that survival of patients with variceal hemorrhage has increased over time,²² which may be attributed to the widespread adoption of non-selective beta-blockers. However, non-selective beta-blockers have several drawbacks - it may have significant adverse effects including systemic hypotension, fatigue and shortness of breath. It is contraindicated, albeit not absolutely, in patients with asthma and insulin dependent diabetes. Further, non-selective beta-blockers impair the patient's quality of life and reduce adherence.¹⁵ Finally, while not all patients achieve sufficient reduction in portal hypertension,²³ HVP is rarely monitored in practice. It remains unknown how many patients endure the side effects of their non-selective beta-blocker while they may not ultimately benefit from it.

The potential deleterious effects of non-selective beta-blockers in patients with advanced hepatic decompensation are increasingly recognized and reflected in the latest Baveno consensus.²⁴ In patients with ascites undergoing large volume paracentesis, non-selective beta-blockers may increase susceptibility to post-paracentesis circulatory dysfunction by limiting the compensatory increase in the cardiac output.²⁵⁻²⁷ A more recent study demonstrated that the use of propranolol was associated with reduced survival at one year in patients with refractory ascites (19% versus 64%)¹³ and in patients with Child-Pugh C and ascites (40% versus 67%).²⁸ Similarly, poor outcomes were reported for non-selective beta-blocker use in patients who have had SBP, including shorter survival (23% versus 36% at one year) and increased incidence of HRS (24% versus 11% at 90 days) and AKI (20% versus 8% at 90 days).²⁹ While acute deterioration in patients with cirrhosis is often precipitated by infection, non-selective beta-blockade was not associated with an increased risk of serious infection in patients with compensated or decompensated cirrhosis.³⁰

The results of this study are in support of the recently proposed 'window' concept for the beneficial effects of non-selective beta-blockers.¹⁵ With regard to renal injury, in patients without ascites, non-selective beta-blockers were beneficial with reduced risk of AKI, whereas in those with ascites, non-selective beta-blockers were harmful with increased risk of AKI (Fig. 3). This observation nicely reconciles the earlier findings of non-selective beta-blockers being protective with those in recent studies in which they led to worse outcomes,^{31,32} as the former studies tended to include less advanced patients compared to the latter ones. According to the window concept, patients with advanced portal hypertensive complications such as refractory ascites and SBP are outside the optimal window and their risks associated with non-selective beta-blockers are higher than their benefits. Our data further suggest that the window might close earlier than previously reported - non-selective beta-blockers may need to be avoided in some patients with ascites prior to the onset of SBP or unresponsiveness to diuretic therapy. In those patients, endoscopic variceal ligation would provide an effective, albeit invasive, alternative to a non-selective beta-blocker for primary or secondary prevention of variceal hemorrhage.

At the population level, our observation may also provide some insights as to the increasing incidence of renal dysfunction in patients awaiting liver transplantation. It is recognized that more recently – ‘in the MELD era’ – increasing number of patients are requiring simultaneous liver and kidney transplantation, reflecting increased prevalence of renal dysfunction in transplant candidates. While the fundamental drivers of this trend include worsening organ shortage and escalating MELD score needed to receive an organ and increasing awareness of the importance of renal function in liver transplant candidates, widespread use of non-selective beta-blockers in patients with advanced portal hypertension may have contributed to the prevalence of renal morbidity.

We do acknowledge that there are limitations to this study. First, in this retrospective study, we were not able to accurately assess severity of ascites and all patients with ascites were lumped together. Patients with mild degree of ascites in whom a non-selective beta-blocker is not detrimental could not be evaluated. Similarly, as we were not able to accurately determine the start and stop dates for non-selective beta blocker usage, it was defined by its presence on the first and last days of observation. Thus, patients who were put on a beta-blocker some time after the baseline may have been misclassified. For these reasons, the authors consider our data to be insufficient to make recommendations about non-selective beta blocker use in patients with ascites, especially those with uncomplicated ascites. Second, because this study was conducted among patients awaiting liver transplantation with preserved renal function, the results may not apply to cirrhotic patients in general or those with chronic kidney disease. Further, the association between non-selective beta blockade and AKI in this study may be confounded by the hemodynamic status of the patient. The direction of effect of beta blockade may not be always predictable, as patients with advanced portal hypertension who remain on non-selective beta-blocker may actually represent a subgroup with a better hemodynamic status. This may explain the observation by Leithead et al.³³ that non-selective beta-blockers in liver transplant candidates were associated with reduced short term (median follow-up 72 days) waitlist death. It may be possible that detailed prospective hemodynamic data such as cardiac index, peripheral vascular resistance, and hepatic venous pressure gradient may provide additional clues to the pathogenesis of AKI in patients receiving a non-selective beta-blocker.

In summary, this study found that non-selective beta-blockers have divergent effects on renal injury depending on the severity of hepatic decompensation. While in patients without ascites, non-selective beta-blockers may help preserve renal function, they increase the risk of AKI in those who already have ascites. This data adds to the growing literature that there is a time window in the natural history of cirrhosis in which non-selective beta-blockers are beneficial to a cirrhotic patient. While more detailed investigation may provide further insights to the renal hemodynamic effects of non-selective beta-blockers in patients in different stages of hepatic decompensation, these data suggest that randomized controlled data are needed to derive data with which to individualize non-selective beta-blocker therapy in cirrhotic patients with portal hypertension.

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Abbreviations

AKI	acute kidney injury
CI	confidence interval
HR	hazard ratio
HVPG	hepatic vein portal pressure gradient
HRS	hepatorenal syndrome
MELD	model for end-stage liver disease
SBP	spontaneous bacterial peritonitis

Fig. 1. Consort diagram depicting selection of cases and controls. Out of the total cohort of 2,361 waitlist registrants, 252 patients developed acute kidney injury. Among them, 205 patients who met the eligibility criteria were matched to 205 controls. AKI, acute kidney injury; NSBB, non-selective beta-blocker

Ascites(+) BB(+)	118	58	38	21	15	8
Ascites(+) BB(-)	150	54	38	32	18	9
Ascites(-) BB(-)	90	41	27	22	17	12
Ascites(-) BB(+)	52	25	17	12	7	5

Fig. 2.

Incidence of acute kidney injury (AKI) according to the presence of ascites and use of non-selective beta-blockers. Among patients with ascites, NSBB users experienced higher incidence of AKI, whereas among those without ascites, the incidence of AKI was much lower in NSBB users. NSBB, non-selective beta-blocker; AKI, acute kidney injury

Fig. 3. The proposed window hypothesis for optimal time period of NSBB use. NSBB, non-selective beta-blocker; GFR, glomerular filtration rate; SBP, spontaneous bacterial peritonitis

Table 1
Baseline Characteristics

	Cases (AKI) (n = 205)	Controls (no AKI) (n = 205)
Age in years, mean $\pm$ SD	52.2 $\pm$ 9.8	52.2 $\pm$ 9.5
Male sex, n (%)	100 (48.8)	117 (57.1)
Race, non-Caucasian, n (%)	34 (16.6)	16 (7.8)
Etiology of cirrhosis, n (%)		
HCV/HBV	64 (31.2)	46 (22.4)
ALD/NASH	48 (23.4)	43 (21.0)
PSC/PBC/AIH	63 (30.7)	89 (43.4)
Others	30 (14.6)	27 (13.2)
Malignancy*, n (%)	20 (9.8)	33 (16.1)
Diabetes, n (%)	16 (7.8)	9 (4.4)
Varices, n (%)	152 (74.1)	142 (69.3)
Total bilirubin, mg/dL	3.3 (1.7-5.9)	2.9 (1.6-4.8)
Prothrombin time, INR	1.2 (1.1-1.5)	1.2 (1.1-1.4)
Creatinine, mg/dL	0.9 (0.8-1.1)	1.0 (0.8-1.1)
Sodium, mmol/L	137 (133-139)	137 (134-140)
MELD score	14 (11-18)	13 (10-17)
MELD-Na score	16.6 (13.0-21.4)	15.5 (12.0-19.0)
Presence of ascites, n (%)	162 (79.0)	106 (51.7)
Use of NSBB, n (%)	94 (45.9)	76 (37.1)

NOTE: Data are presented as median (interquartile range), unless otherwise indicated. *P* values are calculated using student t-test or Wilcoxon rank sum test for continuous variables and chi-square test for categorical variables. For serum creatinine, a case and the matching control had to be within 0.3 mg/dL of each other; for model for end-stage liver disease-Na, within 7points; for age, within 9 years; and for follow-up time.

AKI, acute kidney injury; SD, standard deviation; HCV, hepatitis C virus; HBV, hepatitis B virus; ALD, alcoholic liver disease; NASH, non-alcoholic steatohepatitis; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; INR, international normalized ratio; MELD, model for end-stage liver disease; NSBB, non-selective beta-blocker.

* Includes hepatocellular carcinoma or cholangiocarcinoma.

Table 2
Un-Adjusted Cox Regression Analysis Predicting Acute Kidney Injury

	HR	95% CI	P Value
Age, years	1.00	(0.94, 1.06)	0.93
Male	0.88	(0.53, 1.46)	0.62
Race			
White	Ref		
Other	2.30	(1.16, 4.53)	0.02
Etiology of cirrhosis			
HCV/HBV	Ref		
ALD/NASH	0.74	(0.38, 1.45)	0.38
PSC/PBC/AIH	0.45	(0.24, 0.83)	0.01
Others	0.92	(0.43, 1.97)	0.84
Liver cancer	0.56	(0.27, 1.13)	0.10
Diabetes	1.57	(0.64, 3.86)	0.32
Esophageal varices	1.22	(0.73, 2.03)	0.45
Total bilirubin	1.00	(0.95, 1.04)	0.88
Prothrombin time, INR	0.70	(0.38, 1.27)	0.24
Creatinine	2.81	(1.34, 5.87)	<0.01
Sodium at baseline	0.96	(0.90, 1.03)	0.28
MELD at baseline	1.17	(1.06, 1.28)	<0.01
MELD-Na at baseline	1.55	(1.33, 1.81)	<0.01
Presence of ascites	4.03	(2.36, 6.89)	<0.01
Use of NSBB	1.53	(0.95, 2.48)	0.08

NOTE: *P*-value by Cox proportional hazards model stratifying on matched pairs and adjusting for matching variables to control for residual confounding.

HR, hazard ratio; CI, confidence interval; HCV, hepatitis C virus; HBV, hepatitis B virus; ALD, alcoholic liver disease; NASH, non-alcoholic steatohepatitis; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; INR, international normalized ratio; MELD, model for end-stage liver disease; NSBB, non-selective beta-blocker.

Table 3
Multivariable Cox Regression Analysis for Predicting Acute Kidney Injury

Variable	HR	95% CI	P Value
Age	1.04	0.97-1.12	0.30
Male	0.80	0.44-1.44	0.45
Race			
White	Ref		
Other	1.76	0.80-3.86	0.16
Etiology of cirrhosis			
HCV/HBV	Ref		
ALD/NASH	1.01	0.45-2.29	0.99
PSC/PBC/AIH	0.58	0.29-1.19	0.14
Other	1.26	0.52-3.06	0.61
Presence of liver cancer	0.66	0.28-1.53	0.33
Creatinine	0.05	0.01-0.67	0.02
MELD-Na	1.66	1.36-2.03	<0.01
NSBB with ascites absent	0.19	0.06-0.60	<0.01
NSBB with ascites present	3.31	1.57-6.95	<0.01
Ascites	1.32	0.65-2.68	0.44

NOTE: HR, hazard ratio; CI, confidence interval; HCV, hepatitis C virus; HBV, hepatitis B virus; ALD, alcoholic liver disease; NASH, non-alcoholic steatohepatitis; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; MELD, model for end-stage liver disease; NSBB, non-selective beta-blocker.