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ORIGINAL ARTICLE

Retrospective Cohort Study

Nonselective beta-blocker use is associated with increased hepatic encephalopathy-related readmissions in cirrhosis

Mohammad Amin Fallahzadeh, Sumeet K Asrani, Elliot B Tapper, Giovanna Saracino, Robert S Rahimi

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Mohammad Amin Fallahzadeh, Department of Internal Medicine, Baylor University Medical Center, Dallas, TX 75246, United States

Sumeet K Asrani, Giovanna Saracino, Robert S Rahimi, Division of Hepatology, Baylor University Medical Center, Dallas, TX 75246, United States

Elliot B Tapper, Division of Hepatology, University of Michigan, Ann Arbor, MI 48109, United States

Corresponding author: Mohammad Amin Fallahzadeh, MD, Doctor, Department of Internal Medicine, Baylor University Medical Center, 3500 Gaston Ave, Dallas, TX 75246, United States. aminfa91@gmail.com

Abstract

BACKGROUND

Hepatic encephalopathy (HE) is a neurocognitive condition in cirrhosis leading to frequent hospitalizations. Nonselective beta-blockers (NSBBs) are the mainstay of pharmacologic treatment in cirrhotic patients. We hypothesized that since NSBBs decrease cardiac output and portal flow, the decreased metabolic filtering process of liver parenchyma may lead to increased HE-related hospitalizations.

AIM

To evaluate the impact of NSBB administration on HE-related readmissions in cirrhotic patients.

METHODS

In this retrospective cohort study, we included 393 patients admitted to Baylor University Medical Center for liver-related portal hypertension indications between January 2013 and July 2018. Independent predictors of the first HE-related readmissions were identified using Cox proportional hazards analysis. The cumulative incidence of the first HE-related readmissions between patients receiving NSBBs and not receiving NSBBs was examined using Fine-Gray modeling to account for the competing risk of death or liver transplantation.

RESULTS

The mean age was 58.1 ± 10.2 years and most patients fell into Child class C (49.1%) or B (43.8%). The median Model for End-Stage Liver Disease-Sodium score was 22 (IQR: 11). The cumulative incidence of the first HE-related

readmissions was significantly higher in patients taking NSBBs compared to patients not receiving NSBBs (71.8% *vs* 41.8%, $P < 0.0001$). In multivariate analysis, after adjusting for demographics, markers of liver disease severity, selective beta-blocker, lactulose and rifaximin use, NSBB use [Hazard ratio: 1.74 (95%CI: 1.29-2.34)] was independently associated with the first HE-related readmissions over a median follow-up of 3.8 years.

CONCLUSION
NSBB use is independently associated with increased HE-related readmissions in patients with cirrhosis, regardless of liver disease severity.

Key Words: Altered mental status; Ascites; Esophageal varices; Liver disease; Portal hypertension; Hospitalization

Core Tip: In this study, we evaluated the impact of nonselective beta-blocker (NSBB) administration on hepatic encephalopathy (HE)-related readmissions in patients with Child B or C cirrhosis. After adjusting for markers of liver disease severity, NSBB use was independently associated with the first HE-related readmissions. NSBB use was also an independent predictor of HE-related admissions per person-month.

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INTRODUCTION

Hepatic encephalopathy (HE) is a reversible neurocognitive disorder seen in patients with advanced liver disease[1,2]. It is observed in up to 60% of patients with cirrhosis and is associated with frequent hospitalizations and decreased survival[3-5]. The incidence of HE-related hospitalizations is rising in the United States and imposes a significant economic burden on the healthcare system[6]. In a large population-based cohort, nonselective beta-blocker (NSBB) use was independently linked to HE development[7]. However, the mechanism is unclear.

NSBBs are the mainstay of pharmacologic treatment for portal hypertension and in the prevention of variceal bleeding in cirrhosis[8]. NSBB administration results in reduced cardiac output through inhibition of β1 receptor and splanchnic vasoconstriction *via* antagonism of the β2 receptor, leading to decreased portal inflow[9]. NSBB use may be associated with decreased survival in patients with refractory ascites, increased risk of acute kidney injury, and decreased transplant-free survival in patients with prior spontaneous bacterial peritonitis[10-13]. However, its role in the development of HE-related complications is not known.

We hypothesized that NSBB use contributes to decreased metabolic filtering process of the liver parenchyma, by way of decreased portal inflow (*i.e.*, similar to spontaneous portosystemic shunting), resulting in a secondary increase in HE-related hospitalizations independent of liver disease severity.

MATERIALS AND METHODS

Study population

In this observational, retrospective, single-center study, we examined all adults with cirrhosis following a liver-related hospitalization between January 2013 and July 2018. A hospitalization was considered liver-related if the primary or secondary cause of hospitalization was a portal hypertension-related complication such as HE, ascites, variceal bleeding, or hepatorenal syndrome. Patients were considered to have HE on hospital admission only if they had signs of overt HE (*i.e.*, HE grades II-IV) according to the International Society for Hepatic Encephalopathy and Nitrogen Metabolism and West Haven criteria, respectively[14,15].

Aims

Our primary aim was to examine the association between the use of NSBBs and subsequent HE-related readmissions. Our secondary aim was to identify factors that were predictive of HE-related admissions.

Study variables

We collected information about demographics (age, gender), liver disease [etiology of liver disease, history of hepatocellular carcinoma, esophageal varices (EV) and transjugular intrahepatic portosystemic shunt (TIPS)], physical examination findings in particular heart rate, presence of HE (with or without lactulose +/- rifaximin) and ascites as well as biochemical values including serum creatinine, total bilirubin, international normalized ratio, serum albumin, aspartate aminotransferase, alanine aminotransferase, platelet count and white blood cell count during each admission. The patients were divided into two groups according to whether they were receiving NSBB or not on the first liver-related hospitalization. We also gathered data about selective beta-blocker (SBB) use on the first liver-related hospitalization. Model for End-Stage Liver Disease (MELD), MELD-Sodium (MELD-Na) and Child-Turcotte-Pugh (CTP) scores were calculated for all patients during their first admission. Hospital course and outcome variables (*i.e.*, recurrent HE, death or liver transplantation) were determined during the follow-up period. Patients with a change in their NSBB or SBB status after the first liver-related hospitalization were not included in our study.

Statistical analysis

Continuous data with normal distribution are reported as mean ± SD while continuous data with non-normal distribution are reported as median and ranges (minimum to maximum) or interquartile ranges (IQRs). Independent-samples *t*-test and Mann-Whitney *U* test were used for group comparisons for variables with normal and non-normal distribution, respectively. Categorical data are reported as counts and percentages. Group comparisons for categorical data were made with the χ^2 test.

All analysis began at the landmark time of discharge from the index hospitalization. Cumulative incidence function using Fine-Gray modeling was used to compare the incidence of first HE-related readmissions between the NSBB and no-NSBB groups while taking competing risk of death or liver transplant into account.

Univariate and multivariate Cox regression analyses were done to identify independent predictors of the first HE-related readmissions. Backward elimination technique with $P < 0.10$ for entering the model and $P < 0.05$ for staying in the model was utilized.

To include all of the HE-related admissions, we also determined independent predictors of HE-related hospitalizations per person-month. Due to the overdispersion and right-skewed distribution of this outcome variable, a negative binomial generalized regression model was employed. In this model, total person-months of follow-up was implemented as the offset variable and the follow-up period ended with death, liver transplantation, or end of the study period. The results for the negative binomial generalized regression model were reported as adjusted incidence rate ratios (IRRs) with 95%CIs that represent the relationship between HE-related admissions per person-month and a predictor while considering other covariates.

Subset analysis

To further explore the association of NSBB use and HE-related readmissions, multivariate Cox regression analysis and negative binomial generalized regression model were performed in different subgroups including NSBB *vs* SBB, ascites, EV, MELD-Na score, lactulose and rifaximin subgroups.

A *P* value < 0.05 was considered to be statistically significant. We performed the statistical analyses using SPSS 21 (SPSS Inc) and R statistical software, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). The study was approved by the institutional review board. The statistical review of the study was performed by a biomedical statistician Giovanna Saracino, PhD.

RESULTS

Baseline characteristics

There were 393 patients with a mean age of 58.1 ± 10.2 years and 144 (36.7%) had ascites. The median MELD-Na score was 22 (IQR: 11) and most patients fell into CTP class C (49.1%) or B (43.8%) (Table 1). A total of 143 patients (36.4%) were treated with NSBBs (nadolol, propranolol, or carvedilol) for either prevention of gastrointestinal bleeding or when used for cardiac indications. Nadolol was the most common NSBB used in this study (46.2%) followed by propranolol (43.4%) and carvedilol (10.5%) (Table 2). In the SBB comparison group, 39 patients were given either metoprolol (89.7%) or atenolol (10.3%).

Outcome and follow-up of all patients

The median follow-up time was 3.8 years (IQR: 4.1 years). There were 187 patients (47.6%) who had HE-

Table 1 Baseline characteristics of the patients on the first liver-related hospitalization

	Whole group (*n* = 393)	NSBB group (*n* = 143)	No-NSBB group (*n* = 250)	*P* value
Age, yr	58.1 ± 10.2	57.5 ± 8.8	58.4 ± 11.0	0.39[2]
Gender, male	229 (58.3)	88 (61.5)	141 (56.4)	0.32[3]
Heart rate, bpm	84 (44-161)	76 (44-122)	87 (50-161)	< 0.001[4]
Etiology of liver disease[1]				0.32[3]
Hepatitis C virus	129 (32.8)	55 (38.5)	74 (29.6)	
Alcoholic	124 (31.6)	38 (26.6)	86 (34.4)	
NASH	49 (12.5)	17 (11.9)	32 (12.8)	
Cryptogenic	51 (13.0)	21 (14.7)	30 (12.0)	
Other causes	56 (14.2)	23 (16.1)	33 (13.2)	
CTP score				0.054[3]
A	28 (7.1)	13 (9.1)	15 (6.0)	
B	172 (43.8)	71 (49.7)	101 (40.4)	
C	193 (49.1)	59 (41.3)	134 (53.6)	
MELD score	19 (6-40)	17 (6-39)	19 (6-40)	0.02[4]
MELD-Na score	22 (6-40)	20 (6-39)	22.5 (6-40)	0.005[4]
History of hepatocellular carcinoma	29 (7.4)	8 (5.6)	21 (8.4)	0.31[3]
History of esophageal varices	154 (39.2)	84 (58.7)	70 (28.0)	< 0.001[3]
History of TIPS	47 (12.0)	17 (11.9)	30 (12.0)	0.97[3]
Presence of HE	323 (82.2)	113 (79.0)	210 (84.0)	0.22[3]
Lactulose use	285 (72.5)	107 (74.8)	178 (71.2)	0.44[3]
Rifaximin use	208 (52.9)	81 (56.6)	127 (50.8)	0.26[3]
Presence of ascites	144 (36.7)	50 (35.0)	94 (37.8)	0.58[3]
International normalized ratio	1.5 (1-14)	1.4 (1-4)	1.6 (1-14)	0.003[4]
Platelet count, × 10^{-3}/mm^3	84 (4-515)	72 (15-280)	95 (4-515)	0.002[4]
White cell count, × 10^{-3}/mm^3	6.8 (0.2-51.9)	5.7 (1.3-43.7)	7.7 (0.2-51.9)	< 0.001[4]
Creatinine, mg/dL	1.3 (0.3-33.0)	1.4 (0.4-33.0)	1.3 (0.3-9.3)	0.59[4]
Total bilirubin, mg/dL	2.7 (0.2-137.0)	2.5 (0.2-43.0)	3.1 (0.3-137.0)	0.03[4]
Serum Albumin, g/dL	2.7 (1.0-5.0)	2.8 (2.0-5.0)	2.6 (1.0-5.0)	0.02[4]
Aspartate aminotransferase, U/L	59 (3-4048)	51 (8-677)	67 (3-4048)	< 0.001[4]
Alanine aminotransferase, U/L	39 (10-1180)	34 (13-538)	41 (10-1180)	0.02[4]

Data are presented as *n* (%), mean ± SD or median (range).
[1]The cumulative percent exceeds 100% as some patients had multiple etiologies of liver disease.
[2]*P* calculated by Independent-samples *t*-test.
[3]*P* calculated by χ^2 test.
[4]*P* calculated by Mann-Whitney *U* test.
CTP: Child-Turcotte-Pugh; HE: Hepatic encephalopathy; NSBB: Nonselective beta-blocker; MELD: Model for End-Stage Liver Disease; Na: Sodium; NASH: Non-alcoholic steatohepatitis; TIPS: Transjugular intrahepatic portosystemic shunt.

related readmissions during the follow-up period. The median time between the first admission and future readmission was 1.9 mo (IQR:4.7 mo). Ninety-six patients (24.4%) died and 50 patients (12.7%) received a liver transplant during the study period. The leading causes of death was sepsis [*n* = 32 (33.3%)] followed by cirrhosis and its complications [*n* = 24 (25.0%)], respiratory failure [*n* = 17 (17.7%)] and multi-organ failure [*n* = 8 (8.33%)]. The remaining 15 (15.6%) patients died of other causes.

Table 2 Type, dose and number of patients on nonselective or selective beta-blockers

	Number of patients	Total daily dose (mg)
Nonselective beta-blocker (n = 143)		
Nadolol	66 (46.2)	20 (20-80)
Propranolol	62 (43.4)	30 (10-80)
Carvedilol	15 (10.5)	12.50 (6.25-50.00)
Selective beta-blocker (n = 39)		
Metoprolol	35 (89.7)	50.00 (12.50-200.00)
Atenolol	4 (10.3)	50 (25-100)

Data are presented as n (%) or median (range).

Outcomes according to NSBB therapy

The NSBB group had significantly lower heart rate, MELD-Na score, and platelet count compared with the group not receiving NSBB therapy (Table 1). Further, patients on NSBB therapy had significantly higher rates of presence of EV in comparison with patients not receiving treatment with NSBBs (58.7% *vs* 28%, respectively).

Ninety-one patients (63.6%) in the NSBB group and 96 patients (38.4%) in the no-NSBB group experienced HE-related readmission (P < 0.001). The cumulative incidence of the first HE-related readmissions within 5.5 years was significantly higher in patients taking NSBB compared with patients who were not prescribed NSBB (71.8% *vs* 41.8%, respectively; P < 0.0001) (Figure 1). The mean time to the first HE-related readmission was not significantly different between the two groups (5.3 mo *vs* 4.6 mo in NSBB and no-NSBB groups, respectively, P = 0.5). Furthermore, no significant difference was observed between the two groups regarding the mortality rate [n = 32 (22.4%) in the NSBB *vs* n = 64 (25.6%) in the no-NSBB groups, P = 0.5]. Stratifying the patients according to SBB use, 18 patients (46.2%) with SBB use and 169 patients (47.7%) without SBB use experienced HE-related readmission (P = 0.9).

Factors associated with the first HE-related readmissions

Results of the univariate analysis of factors associated with HE-related rehospitalization are shown in Table 3. After adjustment of demographic characteristics and surrogate markers of liver disease severity, NSBB use was the only independent predictor of the first HE-related readmissions [HR: 1.74 (95%CI: 1.29-2.34)]. This effect was not seen in patients taking SBBs. To further explore this, multivariate Cox regression model was employed in different subgroups of our patients including NSBB *vs* SBB, ascites, EV, MELD-Na score, lactulose, and rifaximin subgroups. NSBB use remained an independent predictor of the first HE-related readmissions in all of these subgroups (Supplementary Tables 1-9).

Factors associated with HE-related admissions per person-month

To further explore our findings, we examined the association of NSBB use with all HE-related admissions. NSBB use was an independent predictor of HE-related admissions per person-month [IRR: 1.50 (95%CI: 1.08-2.07)] alongside other variables including MELD-Na score, history of TIPS, lactulose use and platelet count (Table 4). Similar findings were present with liver-related admissions as the outcome variable. This effect was not observed in patients on SBBs. To further investigate this, negative binomial generalized regression model was performed in different subgroups of our patients including NSBB *vs* SBB, ascites, EV, MELD-Na score, lactulose and rifaximin subgroups. NSBB use remained an independent predictor of HE-related admissions per person-month in all of these subgroups (Supplementary Tables 10-18).

DISCUSSION

Our results demonstrate that patients treated with NSBBs experienced a significantly higher rate of the first HE-related readmissions compared to patients who did not receive NSBBs. Additionally, NSBB group patients had significantly higher cumulative incidence of the first HE-related readmissions compared to patients in the no-NSBB group. Finally, NSBB use was an independent predictor of HE-related admissions per person-month. These findings were persistent even after adjustment for markers of liver disease severity. NSBB use is associated with incident HE[16,17]; however, these data now extend prior research to show that NSBB use is associated with an increased burden of HE-related

Table 3 Univariate and multivariate Cox regression predicting the first hepatic encephalopathy-related readmission

Variable	Unadjusted		Adjusted	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age, yr	1.00 (0.99-1.02)	0.93		
Gender, male	1.03 (0.77-1.38)	0.82		
MELD-Na score (reference: MELD-Na score < 15)				
15 ≤ MELD-Na score ≤ 24	1.26 (0.88-1.79)	0.21		
25 ≤ MELD-Na score ≤ 34	0.89 (0.58-1.36)	0.60		
MELD-Na score > 34	0.38 (0.09-1.55)	0.18		
History of EV, presence of	1.24 (0.93-1.66)	0.15		
History of TIPS, presence of	1.34 (0.89-2.01)	0.16	1.48 (0.98-2.25)	0.065
NSBB use, presence of	1.81 (1.35-2.41)	< 0.001	1.74 (1.29-2.34)	< 0.001
SBB use, presence of	0.90 (0.55-1.46)	0.66		
Lactulose use, presence of	1.28 (0.89-1.82)	0.18		
Rifaximin use, presence of	0.88 (0.66-1.18)	0.40		
Ascites, presence of	1.10 (0.81-1.48)	0.55		
Platelet count, × 10^{-3}/mm^3	0.996 (0.994-0.999)	0.008	0.997 (0.995-1.000)	0.07

EV: Esophageal varices; HR: Hazard ratio; MELD-Na: Model for End-Stage Liver Disease-Sodium; NSBB: Nonselective beta-blocker; SBB: Selective beta-blocker; TIPS: Transjugular intrahepatic portosystemic shunt.

Table 4 Negative binomial generalized regression model predicting hepatic encephalopathy-related admissions per person-month

Variable	IRR (95%CI)	*P* value	B value
Age, yr	0.99 (0.98-1.01)	0.19	-0.010
Gender, male	1.10 (0.82-1.48)	0.54	0.094
MELD-Na score	1.05 (1.03-1.08)	< 0.001	0.052
History of EV, presence of	0.98 (0.72-1.35)	0.92	-0.016
History of TIPS, presence of	1.93 (1.24-3.01)	0.003	0.660
NSBB use, presence of	1.50 (1.08-2.07)	0.015	0.403
SBB use, presence of	0.81 (0.50-1.31)	0.40	-0.208
Lactulose use, presence of	1.47 (1.00-2.15)	0.048	0.384
Rifaximin use, presence of	0.73 (0.53-1.00)	0.050	-0.319
Ascites, presence of	1.26 (0.93-1.72)	0.14	0.233
Platelet count, × 10^{-3}/mm^3	0.997 (0.995-1.000)	0.03	-0.003

EV: Esophageal varices; IRR: Incidence rate ratio; MELD-Na: Model for End-Stage Liver Disease-Sodium; NSBB: Nonselective beta-blocker; SBB: Selective beta-blocker; TIPS: Transjugular intrahepatic portosystemic shunt.

readmissions.

Do NSBBs lead to HE?

There is controversy in the literature regarding the effect that NSBB use has on HE development. Prior studies in early-stage cirrhotic patients reported beneficial to no effect of NSBB on HE development. This includes a cohort of 28 responders to propranolol ± isosorbide mononitrate therapy[18], a randomized trial of propranolol in 20 CTP class A patients[19], and a cohort of 82 patients with cirrhosis [20]. Conversely, other reports indicate an increased risk of HE in NSBB users. In a prospective cohort study of 218 patients with cirrhosis, both NSBB/SBB use was independently associated with a higher

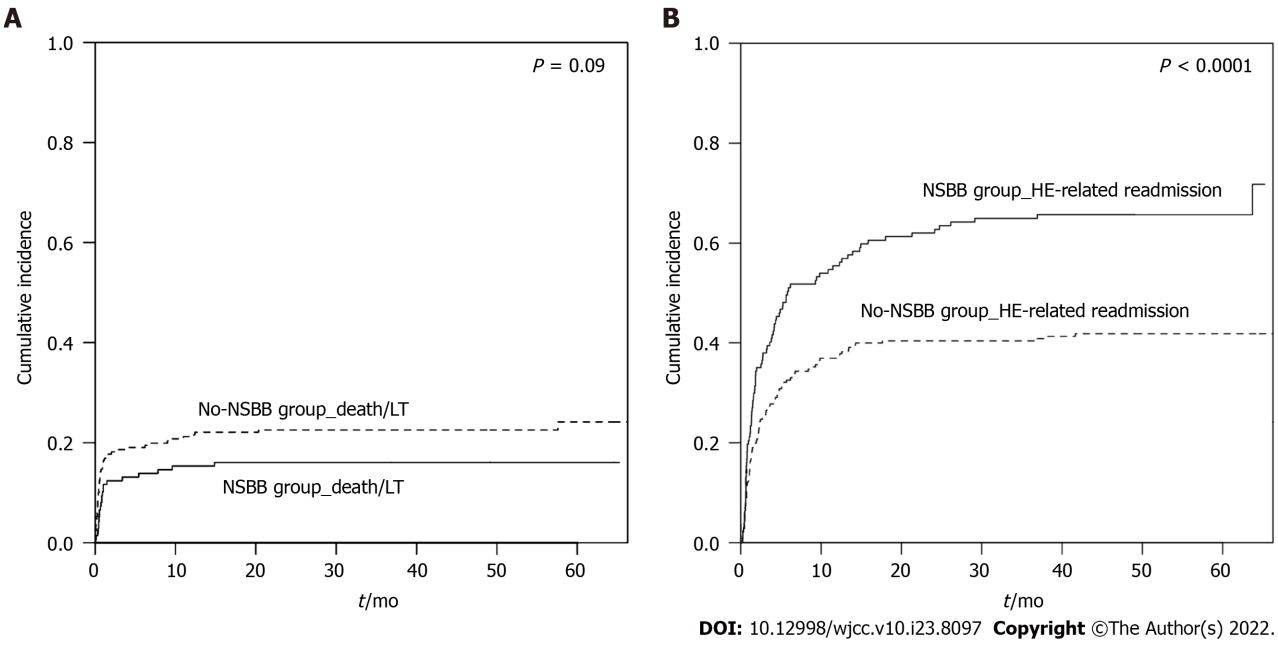

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Figure 1 Cumulative incidence of death or liver transplant in cirrhotic patients with a hepatic encephalopathy-related admission that received nonselective beta-blockers *vs* those who did not (A) and cumulative incidence of the first hepatic encephalopathy-related readmissions in the same groups after adjusting for competing risk of death or liver transplant (B). HE: Hepatic encephalopathy; LT: Liver transplant; NSBB: Nonselective beta-blocker.

rate of minimal HE diagnosis[17]. In a population-based cohort study of 1979 cirrhotic patients, NSBB use was a significant risk factor for incident HE[16]. They hypothesized that NSBB use is a proxy for high-risk varices and severe portal hypertension. The possible explanations for these contradictory research reports of NSBB on HE development are small patient populations, different demographic data, severity of the liver disease, and duration of follow up.

Our data make two major contributions. First, we showed that adjusting for disease severity with granular patient-level data, NSBB use was clearly associated with recurrent HE. Second, our data raise the complexity of the discussion substantially. Our competing risk regression shows that NSBBs are associated with a slightly lower risk of death, confirming the benefits of NSBB use[21,22]. While longer survival avails patients of more opportunity for readmission, our data also shows that NSBBs are associated with a higher burden of readmissions per person-month. Taken together, these data clarify the tradeoffs of NSBB therapy. Therefore, physicians need to be vigilant about NSBB prescription and intensifying therapy.

Reconciling data

We showed that NSBB use in decompensated cirrhotic patients (CTP classes B and C) with high MELD-Na scores increases the risk of HE-related admissions during long-term follow-up. Although no clear explanation for the increase in HE-related admissions with NSBB use can be made, specific comments can be described. Krag *et al*[23] proposed the 'window hypothesis', a certain time frame during the natural course of cirrhosis that only within which NSBB use has a beneficial effect on mortality. The same concept can be true regarding the effect of NSBBs on HE development. In cirrhotic patients with mild to moderate portal hypertension, NSBBs counteract the hyperdynamic cardiovascular state and decrease portal hypertension[23,24]. This likely results in a beneficial effect on HE as it counteracts the most likely pathophysiologic mechanism of HE development; shunting of ammonia towards the brain. This can also be the explanation for the slightly increased survival of the patients taking NSBBs in our study.

With cirrhosis progression, patients develop severe portal hypertension that results in increased cardiac output and decreased systemic vascular resistance. NSBB administration in this stage compromises the systemic perfusion pressure that can ultimately decrease hepatic perfusion[13,23-25]. This will result in increased blood ammonia level shunting systemically to the brain in the context of severe portal hypertension, resulting in the development of HE and increased HE-related readmissions over time.

Our study has certain limitations. Although retrospective in nature, having a relatively large sample size with long-term follow up mitigates the study design. We did not know whether any of the patients had a liver-related hospitalization or a previous HE episode before inclusion in the study. However, adjusting for disease severity did not change the results. Although the exact start and end dates and

compliance with NSBB and SBB use in all cases and hence the association between duration of NSBB use and risk of HE-related readmissions were not determined, stable estimates across a variety of subsets showed similar results. Furthermore, blood pressure, ammonia levels, precipitant factors for HE, association of NSBB use with different overt HE grades, indications/contraindications for NSBB use and diuretic/proton pump inhibitor use were not explored in our study. Due to limited sample size for an individual NSBB medication and lack of a universal dose-conversion guideline for different NSBBs, a meaningful analysis exploring the association of different doses of NSBBs and risk of HE-related readmissions could not be performed in our study. Although HVPG measurements would have been useful, obtaining HVPG data in a retrospective fashion on our patients was impractical. However, future trials could help delineate the exact HVPG level at which HE readmissions occur in relation to heart rate and NSBB use. Therefore, we believe that our study provides a foundation to guide future prospective trials, allowing pharmacologic comparisons to further delineate the association between NSBB, SBB and HE-related readmissions.

CONCLUSION

In conclusion, we show that NSBB use is independently associated with increased HE-related readmissions in patients with cirrhosis, regardless of liver disease severity or biochemical abnormalities. Further prospective studies are needed to determine the impact of NSBBs on HE and other portal hypertension complications.

ARTICLE HIGHLIGHTS

Research background

Hepatic encephalopathy (HE) is a cirrhosis complication leading to frequent hospitalizations and imposes a significant economic burden on the healthcare system. Nonselective beta-blockers (NSBBs) are the mainstay of pharmacologic treatment for portal hypertension and in the prevention of variceal bleeding in cirrhosis. The role of NSBBs in the development of HE-related complications is not known.

Research motivation

We hypothesized that since NSBBs decrease cardiac output and portal flow, the decreased metabolic filtering process of liver parenchyma may lead to increased HE-related hospitalizations. If there is a signal that NSBB use is associated with HE-related hospitalizations, further multicenter trials are warranted to explore the impact of NSBBs on HE and other portal hypertension complications.

Research objectives

The main objective of this study was to evaluate the impact of NSBB administration on HE-related readmissions in cirrhotic patients.

Research methods

We performed an observational, retrospective, single-center cohort study including 393 patients with cirrhosis admitted to Baylor University Medical Center for liver-related portal hypertension indications between January 2013 and July 2018. Independent predictors of the first HE-related readmissions were identified using Cox proportional hazards analysis. The cumulative incidence of the first HE-related readmissions between patients receiving NSBBs and not receiving NSBBs was examined using Fine-Gray modeling to account for the competing risk of death or liver transplantation.

Research results

In a cohort of patient with mostly Child class C (49.1%) or B (43.8%) cirrhosis, the cumulative incidence of the first HE-related readmissions was significantly higher in patients taking NSBBs compared to patients not receiving NSBBs (71.8% *vs* 41.8%, $P < 0.0001$). In multivariate analysis, after adjusting for demographics, markers of liver disease severity, selective beta-blocker, lactulose and rifaximin use, NSBB use [Hazard ratio: 1.74 (95%CI: 1.29-2.34)] was independently associated with the first HE-related readmissions over a median follow-up of 3.8 years. These results warrant further multicenter clinical trials to explore the impact of NSBBs on HE and other portal hypertension complications.

Research conclusions

NSBB use is patients with advanced cirrhosis is independently associated with increased HE-related readmissions, regardless of liver disease severity or biochemical abnormalities. This can be due to the role of NSBB use in decreasing the systemic perfusion pressure that can ultimately lead to a decrease in hepatic perfusion in advanced cirrhosis that will result in an increased blood ammonia level shunting

systemically to the brain.

Research perspectives

As this study was a retrospective study, future prospective cohort and randomized clinical trials are warranted to explore the impact of NSBBs on HE and other portal hypertension complications.

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FOOTNOTES

Author contributions: Fallahazdeh MA, Asrani SK and Rahimi RS designed the research study; Fallahzadeh MA, Asrani SK, Tapper EB, Saracino G and Rahimi RS performed the acquisition, analysis and interpretation of the data; Fallahzadeh MA, Asrani SK and Rahimi RS drafted the manuscript and all authors contributed to revising the manuscript critically; all authors have read and approved the final manuscript.

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ORCID number: Mohammad Amin Fallahzadeh 0000-0002-4308-9856; Sumeet K Asrani 0000-0001-9174-5670; Elliot B Tapper 0000-0002-0839-1515; Giovanna Saracino 0000-0001-9323-5623; Robert S Rahimi 0000-0002-2595-1852.

Corresponding Author's Membership in Professional Societies: American Association for the Study of Liver Diseases, No. 224919.

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