Title

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Journal

Clinical Transplantation, 32(12)

ISSN

0902-0063

Authors

Fu, Hong
Sun, Kai
Li, Jun
et al.

Publication Date

2018-12-01

DOI

10.1111/ctr.13422

Peer reviewed

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Received: 6 July 2018 | Revised: 7 September 2018 | Accepted: 7 October 2018

DOI: 10.1111/ctr.13422

ORIGINAL ARTICLE

WILEY Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research

Preoperative beta blockade and severe intraoperative bradycardia in liver transplantation

Hong Fu[1,2] | Kai Sun[3] | Jun Li[4] | Weiyi Gong[5] | Vatche Agopian[6] | Min Yan[3] | Ronald W. Busuttil[6] | Randolph H. Steadman[2] | Victor W. Xia[2]

[1]Department of Anesthesiology, Chongqing Traditional Chinese Medicine Hospital, Chongqing, China

[2]Department of Anesthesiology and Perioperative Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California

[3]Department of Anesthesiology, Second Affiliated Hospital of Zhejiang University of School of Medicine, Hangzhou, Zhejiang, China

[4]Department of Anesthesiology, Mianyang Central Hospital, Mianyang City, Sichuan Province, China

[5]Department of Anesthesiology, Baoan District People's Hospital, Shenzhen, China

[6]Department of Surgery, David Geffen School of Medicine at UCLA, Los Angeles, California

Correspondence
Victor W. Xia, Department of Anesthesiology and Perioperative Medicine, Ronald Reagan UCLA Medical Center, David Geffen School of Medicine at UCLA, University of California, Los Angeles, CA.
Email: vxia@mednet.ucla.edu

Funding information
Support was provided solely departmental sources.

Abstract

Nonselective Beta blockade (NSBB) is commonly prescribed for liver transplantation (LT) candidates, but its impact on intraoperative hemodynamics is not well understood. In this study, we investigated if preoperative NSBB was associated with severe bradycardia during LT and if severe intraoperative bradycardia was associated with 30-day mortality. Adult patients undergoing LT between 2005 and 2014 were included. Propensity matching was used to control selection bias. Intraoperative hemodynamics were compared between patients with and without preoperative NSBB. Univariate and multivariate methods were used in statistical analysis. Of 1452 patients, 370 who received preoperative NSBB were matched in a 1:1 ratio with those who did not. Propensity matching eliminated all significant differences between the two groups. Patients who received preoperative NSBB had a significantly higher incidence of severe intraoperative bradycardia compared with the non-BB group (9.6% vs 3.2%, $P = 0.001$, OR 2.95, 95% CI 1.42-6.12, $P = 0.004$). Intraoperative hypotension and postreperfusion syndrome were not significantly different between the two groups. Severe intraoperative bradycardia was associated with increased 30-day mortality. In conclusion, preoperative NSBB was associated with severe intraoperative bradycardia in LT. In patients who receive preoperative NSBB, severe intraoperative bradycardia should be closely monitored in LT. Further studies assessing safety of preoperative NSBB and intraoperative bradycardia in LT are warranted.

KEYWORDS
beta blockade, bradycardia, liver transplantation, outcome, postoperative complication, risk factor

1 | INTRODUCTION

Beta blockade (BB) is a class of drugs commonly used in patients before liver transplantation (LT).[1-4] In fact, nonselective BB (NSBB) is the principal drug for portal hypertension and currently is the only drug class recommended for the long-term therapy.[5] As LT candidates have more advanced liver disease at the time of transplant, NSBB is more likely to be encountered in the perioperative period.[6] Nonselective BB has a wide range of effects on patient's hemodynamics.[2,3,5] It blocks catecholamine binding on the beta-2 receptors in the splanchnic vasculature, leading to lower portal pressure and decreased variceal bleeding. It also acts on beta-1 receptors in the cardiovascular system, resulting in attenuated responses to surgical stress, low heart rate, blood pressure, and cardiac output.

The wide range hemodynamic effects of preoperative BB have raised a concern that its preoperative use may lead to excessive sympathetic attenuation and adverse hemodynamic changes in patients undergoing LT.[7] Clinical trials in noncardiac surgery have shown that

preoperative BB is associated with adverse intraoperative hemodynamic changes including bradycardia and hypotension; both are further linked to poor postoperative outcomes.[8-10] Studies in LT patients have also shown that hyperdynamic state of patients undergoing LT can be attenuated by preoperative BB.[7,11] Despite these, understanding the exact relationship between preoperative NSBB and intraoperative hemodynamics is difficult. This is because first the types of BB (selective BB vs NSBB) and the primary indication (cardiac disease vs portal hypertension) are different in the clinical trials compared with those in LT. Secondly, compared with patients undergoing noncardiac surgery, LT patients may be more susceptible to negative hemodynamic impact imposed by preoperative BB due to end-stage liver disease. Thirdly, although previous studies show the relation between preoperative BB and intraoperative attenuation during LT, values of the previous studies are significantly limited by small number of patients enrolled, mixture of selective and nonselective BB, study design flaws and statistical constrains.[7,11]

In the present study, we used our prospectively collected large database to investigate whether preoperative use of NSBB was associated with severe intraoperative bradycardia in LT and if severe intraoperative bradycardia was associated with 30-day postoperative mortality.

2 | PATIENTS AND METHODS

This study was approved by the institutional review board (IRB# 11-003058) of the University of California Los Angeles (UCLA). Consecutive patients who underwent LT at Ronald Reagan UCLA Medical Center between October 2005 and September 2014 were included except for those whose age was <18 years old and whose pretransplant diagnosis was acute liver failure. Patients who received selective BB were also excluded from analysis.

Preoperatively, patients were managed by a multidisciplinary team and BB was prescribed by either primary physicians or consulting specialists. Anesthetic management and surgical technique followed our institutional protocols, which has been described in detail previously.[12,13] Briefly, anesthetic techniques consisted of anesthetic induction by intravenous agents and maintenance by combined inhalational and intravenous anesthetics. In addition to standard monitors, invasive monitors including intra-arterial catheter and the Swan-Ganz catheter for central venous pressure, pulmonary artery pressure and cardiac output were routinely used. Intraoperative transesophageal echocardiography was at the discretion of the anesthesiologist. Intraoperative venovenous bypass and hemodialysis were selectively used and determined by the attending surgeon and the anesthesiologist. Blood products included packed red blood cells, fresh frozen plasma (FFP), platelets, and cryoprecipitate. Transfusion of red blood cells and FFP were administered via a rapid transfusion device. Vasoactive agents including phenylephrine, norepinephrine, and vasopressin were used through intravenous bolus or continuous infusion. Intraoperative bradycardia was treated with pharmacologic agents including glycopyrrolate, atropine, and epinephrine. Intraoperative hypotension was managed by volume replacement and vasoactive agents.

Perioperative data including demographics, pretransplant comorbidity, etiology of liver disease, Model of End-stage Liver Disease (MELD) score, laboratory values, duration of surgery, transfusion of blood products, and postreperfusion syndrome (PRS) were extracted from the UCLA transplant database where the data were prospectively collected and stored. Data related to the preoperative BB therapy including type of the drugs, primary indications, doses, and duration of the BB therapy were collected by reviewing medical charts, pharmacy records, and physician's notes. Patients were divided into two groups: NSBB and non-BB groups. Patients who used NSBB at least 7 days and up to immediately before LT were included in the NSBB group.

Hemodynamic parameters measured in the study included intraoperative heart rate, blood pressure, and PRS. The data on heart rate and arterial blood pressure were obtained by reviewing our electronic anesthesia records. Bradycardia was defined as the lowest recorded heart rate was <60 beats per minute (bpm) for 10 minutes or longer and severe bradycardia as the lowest heart rate <50 bpm for 10 minutes or longer. Hypotension was defined as the lowest recorded mean arterial blood pressure (MAP) <60 mm Hg for at least 10 minutes. The relations of bradycardia and hypotension to reperfusion of the liver graft were recorded as well. PRS was defined as blood pressure decreased 30% from prereperfusion baseline for at least 1 minute within 5 minutes after reperfusion of the liver graft. Mortality was all-cause mortality within 30 days after LT.

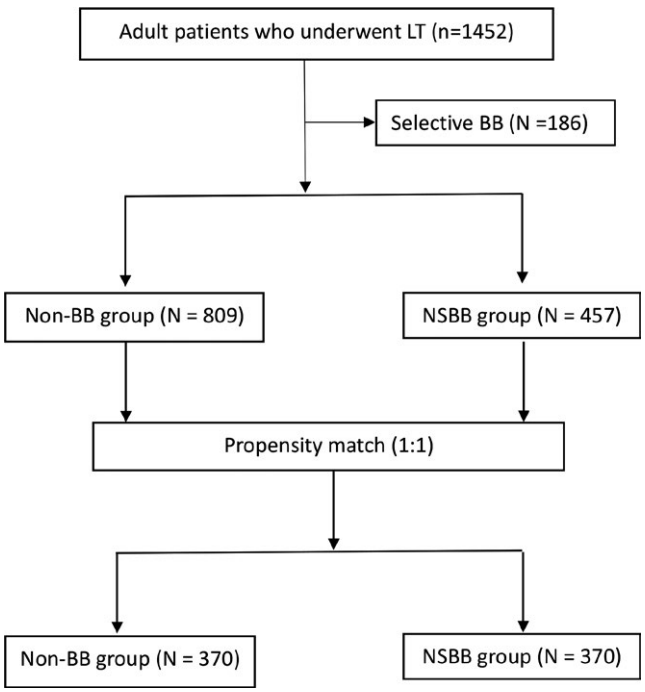

FIGURE 1 Flowchart. Of 1266 adult patients undergoing liver transplantation, 370 patients who received nonselective beta blockade (NSBB) were matched with 370 patients who did not received BB before transplantation

Statistical analysis comparing variables between the two groups was performed by using Pearson's chi-square, Fisher exact, Student's *t* or Mann-Whitney tests. Variables that showed a potential significance ($P < 0.1$) during univariate analyses were included in multivariable logistic regression. Patients with and without BB therapy were matched by propensity scores. The propensity score was generated from variables that occurred before transplant and had a potential to generate selection bias or influence the outcome. Patients were matched with nearest neighboring matching in a 1 to 1 ratio. The caliper was limited with 0.1. Intraoperative hemodynamic complications and postoperative mortality were compared between the NSBB and non-BB groups after match. Independent risk factors for intraoperative hemodynamic complications were identified by using a multivariable logistic regression. Survival was assessed by Kaplan-Meier survival analysis with log-rank analysis. Factors that were associated with mortality were analyzed by multivariate Cox survival analysis. All multivariate analysis used after-match cohort. Hazard ratio (HR) or odds ratio (OR) and 95% of confidence interval (95% CI) were reported. Data were presented by mean ± standard deviation (SD) for continuous variables or percentages for categorical variables. *P* values <0.05 were considered significant. Analyses were performed using Statistical Package for Social Science 24.0 for Windows (IBM Corp., Armonk, NY).

3 | RESULTS

One-thousand four hundred and fifty-two adult patients with chronic liver failure underwent LT during the study period. Of 1452 patients, 186 who received selective BB were excluded, leaving 1266 patients in the study (Figure 1). Mean age of the patients was 54.9 ± 10.5 with 65.3% of male. Mean MELD score was 31.9 ± 7.8. Chronic viral hepatitis was the primary indication for LT, followed by alcoholic cirrhosis and nonalcoholic steatohepatitis. Of 1266 patients, 457 patients (36.1%) received NSBB therapy in the preoperative period (Figure 1). Propranolol and nadolol were most common and consisted of 96.0% of the NSBB usage (Figure 2). Mean doses of propranolol and nadolol were 15.4 ± 11.2 and 22.8 ± 12.9 mg, respectively.

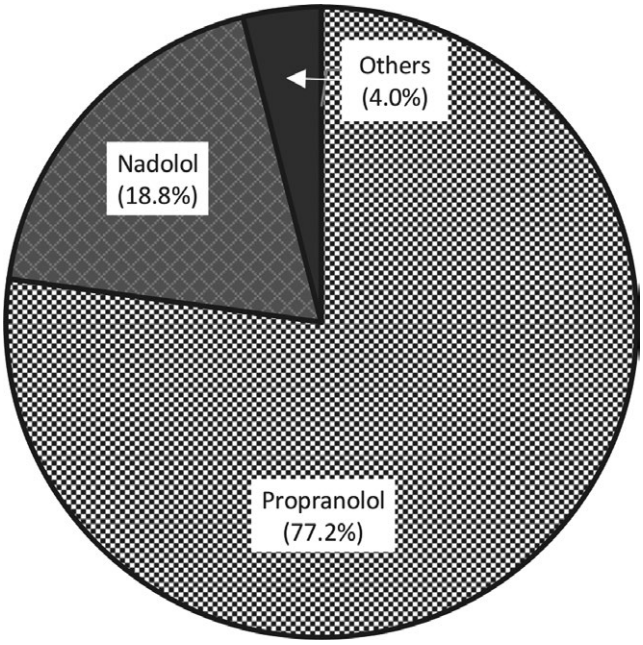

FIGURE 2 Distribution of nonselective beta blockade used preoperatively

Patients who did and did not receive preoperative NSBB therapy were significantly different in preoperative characteristics (Table 1). Patients in the NSBB group were significantly older, had higher body weight, more male patients and more diabetes mellitus. However, MELD score, history hypertension, coronary artery disease,

TABLE 1 Selected preoperative variables before matching

Variables	Non-BB group (N = 809)	NSBB group (N = 457)	*P*
Age (years)	54.2 ± 11.3	56.0 ± 8.8	0.002
Male gender (%)	61.2	72.3	<0.001
Body mass index (kg/m^2)	27.9 ± 9.0	28.1 ± 10.9	0.820
Body weight (kg)	78.8 ± 18.6	81.8 ± 20.8	0.014
MELD score	31.9 ± 7.9	31.8 ± 7.6	0.945
History of hypertension	28.6	32.7	0.133
Coronary artery disease	7.8	8.8	0.530
Diabetes mellitus	26.5	33.0	0.016
Preoperative dialysis	37.6	35.7	0.506
Preoperative intubation	20.1	21.1	0.677
Preoperative pressor requirement	14.7	14.1	0.779
Presentation of encephalopathy	41.9	44.7	0.338
Alcoholic cirrhosis	21.9	25.5	0.159
Presence of ascites	45.4	47.7	0.423
Baseline laboratory values			
Hematocrit (%)	29.2 ± 5.8	28.7 ± 5.9	0.148
International normalized ratio	1.7 ± 0.70	1.9 ± 1.5	0.125
Creatinine (mol/L)	1.7 ± 1.5	1.8 ± 1.4	0.544
Potassium (mol/L)	3.9 ± 0.63	3.9 ± 0.6	0.713
Sodium (mol/L)	136.9 ± 5.0	137.1 ± 4.9	0.428

BB, beta blockade; NSBB, nonselective BB.
Data presented as mean ± SD or percentage.

requirement of preoperative dialysis, and the use of preoperative vasoactive agents were not significantly different between the two groups. Seven pretransplant variables (age, gender, body mass index, MELD score, history of diabetes, history of hypertension, and history of coronary artery disease) were used to generate propensity scores for the matching. A total of 370 patients in the NSBB group were matched with 370 patients in the non-BB group. After-match comparison showed that all pre-matched differences between the two groups were eliminated (Table 2).

TABLE 2 Selected preoperative variables after matching

Variables	Non-BB group (N = 370)	NSBB group (N = 370)	*P*
Age (years)	55.6 ± 10.5	56.0 ± 8.6	0.633
Male gender	70.3	71.9	0627
Body mass index (kg/m^2)	28.1 ± 9.6	28.1 ± 11.2	0.992
Body weight (kg)	80.3 ± 17.1	81.4 ± 20.9	0.471
Height (cm)	170.0 ± 11.8	169.9 ± 11.7	0.861
MELD score	32.4 ± 7.7	32.1 ± 7.5	0.660
History of hypertension	31.1	31.6	0.874
Coronary artery disease	7.8	8.1	0.892
Diabetes mellitus	26.8	32.7	0.077
Presence of ascites	44.7	46.4	0.635
Preoperative dialysis	36.7	33.9	0.425
Preoperative intubation	18.8	19.6	0.779
Preoperative pressor	15.9	12.9	0.252
Presence of encephalopathy	41.2	44.0	0.442
Cold ischemia time (min)	410.3 ± 144.9	421.4 ± 146.0	0.304
Warm ischemia time (min)	42.4 ± 10.9	42.7 ± 9.9	0.656
Baseline laboratory values			
Hematocrit (%)	29.5 ± 6.2	29.0 ± 6.0	0.512
International normalized ratio	1.7 ± 0.6	1.8 ± 0.7	0.087
Creatinine (mol/L)	1.8 ± 1.4	1.7 ± 1.2	0.931
Potassium (mol/L)	3.9 ± 0.6	3.9 ± 0.6	0.942
Sodium (mol/L)	136.8 ± 4.9	137.2 ± 4.8	0.251

BB, beta blockade; NSBB, nonselective BB.
Data presented as mean ± SD or percentage.

Comparison of intraoperative hemodynamics using after-match data showed that intraoperative heart rates in the NSBB and non-BB groups were significantly different. As shown in Figure 3, there was a downward shift of the lowest heart rate in the NSBB group (60.6 ± 11.3 bpm) compared with the non-BB group (65.3 ± 13.1 bpm, $P < 0.001$). The overall incidence of intraoperative bradycardia and severe bradycardia was 35.6% and 6.7%, respectively. Patients treated with preoperative NSBB had significantly higher incidences of bradycardia and severe bradycardia (43.0% and 9.6%) compared with patients without BB (26.5% and 3.2%, both $P = 0.001$, Table 3). Severe bradycardia in occurred most in the prereperfusion period compared with in the postreperfusion period in overall patients (6.7% vs 2.3%) as well as in patients received preoperative NSBB (8.0% vs 2.9%). Severe bradycardia was significantly different in the prereperfusion period (8.0% vs 1.9%, $P < 0.001$), but not in the postreperfusion period (2.9% vs 1.9%, $P = 0.280$), as compared the NSBB with the non-BB group. In a multivariate logistic analysis including preoperative and intraoperative factors, preoperative NSBB therapy was an independent risk factor for development of severe intraoperative bradycardia (OR 2.95, 95% CI 1.42-6.12, $P = 0.004$, (Table 4). In contrast, the use of intraoperative pressors was negative risk factor for development of intraoperative bradycardia (OR 0.36, 95% CI 0.19-0.67, $P = 0.001$). Intraoperative

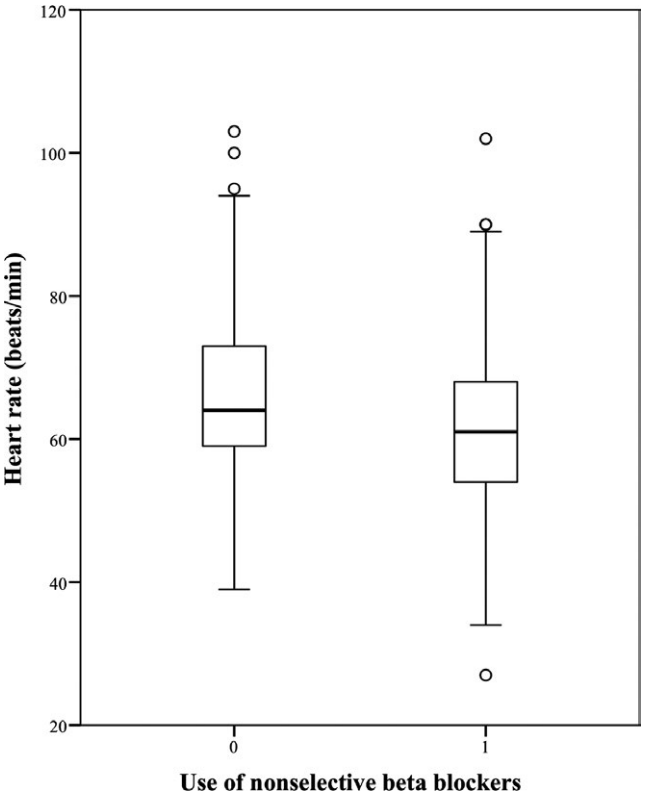

FIGURE 3 Mean intraoperative heart rates (lowest heart recorded for at least 10 min) between the non-BB (67.6 ± 11.5 bpm) and nonselective beta blockade (NSBB) groups (62.1 ± 11.7 bpm, $P < 0.001$). (note: 0 indicating the non-BB group and 1 indicating the NSBB group)

TABLE 3 Intraoperative hemodynamics between after-match groups

Variables	Non-BB group (n = 370)	NSBB group (n = 370)	*P*
Lowest recorded heart rate (beat per minute)	65.3 ± 13.1	60.6 ± 11.3	<0.001
Bradycardia (HR < 60 bpm, %)	26.5	43.0	0.001
Severe bradycardia (HR < 50 bpm, %) in the overall intraoperative period	3.2	9.6	0.001
Severe bradycardia (HR < 50 bpm, %) in the prereperfusion period	1.9	8.0	<0.001
Severe bradycardia (HR < 50 bpm, %) in the postreperfusion period	1.9	2.9	0.280
Lowest mean arterial blood pressure (mm Hg)	55.3 ± 8.0	55.0 ± 6.7	0.700
Hypotension (MAP ≤ 50 mm Hg, %)	18.2	19.2	0.758
Postreperfusion syndrome (%)	16.8	13.9	0.278

BB, Beta blockade; NSBB, nonselective BB; HR, heart rate; MAP, mean arterial pressure.

TABLE 4 Univariate and multivariable analysis for severe bradycardia

	Univariable analysis			Multivariable analysis		
Risk factors	OR	95% CI	*P*	OR	95% CI	*P*
Use of preoperative NSBB	3.21	1.57-6.57	0.001	2.95	1.42-6.12	0.004
Preoperative dialysis	0.39	0.17-0.88	0.023			
Preoperative pressors	0.13	0.02-0.098	0.048			
Preoperative intubation	0.30	0.09-0.99	0.049			
Intraoperative pressors in continuous infusion	0.36	0.20-0.68	0.002	0.36	0.19-0.67	0.001
Intraoperative transfusion of fresh frozen plasma (per unit)	0.97	0.95-0.99	0.032			
Intraoperative transfusion of red blood cell (per unit)	0.98	0.95-1.00	0.094			

CI, confidence intervals; NSBB, nonselective beta blockade; OR, odds ratio.

hypotension and PRS was not significantly different between the NSBB and non-BB groups (Table 3).

Overall 30-day mortality for all patients in our study was 4.0%. Patients treated with and without preoperative NSBB had similar 30-day mortality (5.1% vs 3.0%, $P = 0.132$). However, patients who developed severe intraoperative bradycardia had significantly higher 30-day mortality compared those without severe intraoperative bradycardia (8.9% vs 3.0%, $P = 0.036$; Figure 4). Majority of death occurred in the postoperative period since only two patients, one in each group (yes or no for severe intraoperative bradycardia) died in the intraoperative period. Severe intraoperative bradycardia was an independent risk factor for both 30-day mortality (HR 6.93, 95% CI 2.15-22.32, $P = 0.001$). Other risk factors for 30-day mortality included requirement of preoperative pressors and intraoperative FFP transfusion (Table 5).

4 | DISCUSSION

In this large retrospective study of 1266 adult patients, we showed that NSBB was used in a large percentage of patients before LT. Preoperative NSBB was associated with an increased risk of

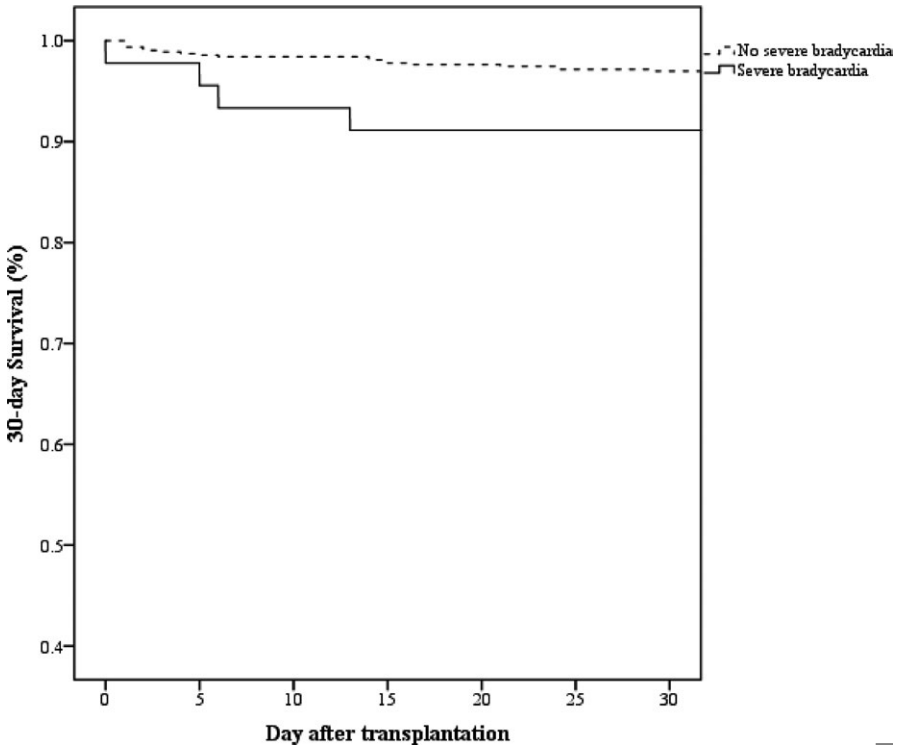

FIGURE 4 Kaplan-Meier survival analysis shows patients who developed severe intraoperative bradycardia had significantly higher 30-d recipient mortality compared with those who did not develop severe intraoperative bradycardia (log-rank test $P = 0.032$)

TABLE 5 Univariate and multivariable Cox survival analysis for postoperative 30-d mortality

	Univariable analysis			Multivariate analysis		
Risk factors	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Preoperative pressor	6.99	3.49-14.01	<0.001	6.74	2.70-16.85	<0.001
Encephalopathy	4.67	2.02-10.86	<0.001			
Preoperative intubation	3.26	1.62-6.55	0.001			
Preoperative dialysis	4.11	1.94-8.67	<0.001			
Intraoperative transfusion of fresh frozen plasma (unit)	1.02	1.01-1.03	<0.001	1.02	1.01-1.03	0.003
Intraoperative pressors in bolus	2.45	1.19-5.04	0.015			
Severe bradycardia	3.07	1.04-9.02	0.042	6.93	2.15-22.32	0.001

CI, confidence intervals; HR, harzard ratio.

developing severe bradycardia during LT and severe intraoperative bradycardia was associated with posttransplant 30-day mortality. Preoperative NSBB was not associated with intraoperative hypotension or PRS. In patients receiving preoperative NSBB, severe intraoperative bradycardia should be closely monitored in patients undergoing LT.

Our findings have clinical implications in the perioperative management in LT. Patients with end-stage liver disease often have a compensatory hyperdynamic state, presented by relatively fast heart rate, along with low systemic vascular resistance and high cardiac output.[11] During LT surgery when hemodynamic fluctuation is frequently seen, the ability to maintain adequate cardiac output during LT is paramount.[12] Nonselective BB, like selective BB, when used for portal hypertension in the preoperative period, has the similar potential to lead to the development of intraoperative bradycardia. Despite the similarities, a significant difference should be noted. Selective BB is primarily for cardiac diseases, slow heart rates may provide a favorable balance between oxygen supply and demand, particularly in patients with ischemic heart disease.[8] In contrast, NSBB is used primarily for portal hypertension, benefits of bradycardia may be questionable and severe intraoperative bradycardia may be harmful.

Cause of intraoperative bradycardia in LT is multifactorial[14-16] and identification of exact cause is beyond scope of this investigation. However, our study may exclude some suspects. Majority of severe bradycardia in our study occurred before reperfusion, suggesting

that the bradycardic development is unlikely caused solely by PRS or reperfusion related acidosis, hyperkalemia, and electrolyte disturbances. In addition, severe hypotension was not significantly different between the two groups, excluding hypotension from likely causes. It is possible that there were many pro-bradycardia factors present in patients in both groups, preoperative NSBB may exacerbate the pro-bradycardic effects and facilitate the development of intraoperative bradycardia.

In contrary to studies in noncardiac surgery reporting that BB is associated with both intraoperative bradycardia and hypotension, we could not show the relationship between preoperative NSBB and intraoperative hypotension. This discrepancy further highlights the differences between LT and noncardiac surgery. Liver transplantation surgery has frequent and severe hypotension due to massive blood loss, coagulopathy, and cross-clamp of large vessels. It is possible that these factors have strong hypotensive effects, undermining the effects of NSBB. Similarly, preoperative NSBB was not found to associate with development of PRS in our study. This may be related to facts that PRS primarily reflects graft quality, extent of ischemia/reperfusion injury, and perioperative management.

NSBB, primarily used for portal hypertension and variceal bleeding, has clear preoperative benefits.[2] Our study has shown that preoperative NSBB has neither beneficial nor harmful effects on immediate postoperative survival. This result disputes reports from previous studies claiming that preoperative BB is associated with increased survival after LT.[17,18] It should point out that a small sample size and mixture of selective and nonselective BB in the previous studies make it difficult to interpret the results.[17,18] Nonselective BB may have another potential side effect as a recent study show that NSBB is associated with acute kidney injury in LT patients.[19]

Despite the potential intraoperative hemodynamic side effects of preoperative NSBB, abrupt cessation of NSBB therapy before LT is not recommended. The acute withdrawal of BB therapy can lead to complications.[20] Abrupt cessation of BB therapy can result in rising portal pressure, variceal bleeding, accelerated angina, and myocardial infarction even in patients without previously diagnosed coronary artery disease.[20] These are presumably due to rebound sympathetic activity resulting in a hyperadrenergic state. While preoperative BB therapy should continue, close monitoring intraoperative bradycardia, especially severe bradycardia, in LT is recommended. Severe bradycardia should be avoided during LT when possible. If severe intraoperative bradycardia occurs, proper interventions should be implemented. The use of intraoperative pressors is associated with decreased incidence of severe bradycardia in our study. Therefore, the use of vasoactive drugs with positive chronotropic effect is recommended, particularly in patients with a high risk of development of intraoperative bradycardia.

Although our study is large with propensity controls, limitations are worth mentioning. First, it was a retrospective study, which inherited all shortcomings of the retrospective design. Second, this was a single center study. Extrapolation of our findings should be cautious. Third, although we used statistical method to control selection bias, there was no guarantee that all bias were eliminated. Fourthly, in addition to MELD score, other indexes of overall severity of illness such as APACHE and SOFA scores have significant impact on patient outcome. Unfortunately, our dataset did not include such data, therefore, they were not included in our analysis. Finally, the management of posttransplant complications was not standardized, and this inevitably introduced some bias into analysis.

In summary, in this large retrospective study, we showed that NSBB was commonly used before LT. Preoperative NSBB was associated with an increased incidence of intraoperative bradycardia. Severe intraoperative bradycardia was associated with 30-day mortality after LT. In patients who receive preoperative NSBB, severe intraoperative bradycardia should be closely monitored. Further studies to assess safety of preoperative NSBB therapy and intraoperative hemodynamics in LT are warranted.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONS

FH participated in the study concept, data collection, data analysis, and article preparation. SK participated in the data analysis and article preparation. JL participated in the data analysis and article preparation. WG participated in the data analysis and article preparation. VA participated in the data collection and article preparation. MY participated in the concept and article preparation. RWB participated in the study concept and article preparation. RHS participated in the study concept and article preparation. VWX participated in the study concept, data collection, data analysis, and article preparation.

ORCID

Victor W. Xia http://orcid.org/0000-0003-1182-3179

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How to cite this article: Fu H, Sun K, Li J, et al. Preoperative beta blockade and severe intraoperative bradycardia in liver transplantation. *Clin Transplant*. 2018;e13422. https://doi.org/10.1111/ctr.13422