Perioperative Beta-blocker and Statin use in Patients with Coronary Artery Disease Undergoing Orthotopic Liver Transplantation

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Abstract

Background: In patients that undergo Orthotopic Liver Transplantation (OLT), the presence of Coronary Artery Disease (CAD) is associated with worse short- and long-term outcomes. With reported 3-year mortality rates up to 50%, recent efforts have focused on ways to reduce perioperative cardiovascular risk in this population. While continuation of Beta-Blocker (BB) and statin therapy has been shown to benefit patients with known CAD undergoing intermediate or high-risk noncardiac surgery, it is unknown whether these therapies benefit patients with CAD undergoing OLT.

Methods: We retrospectively identified 45 patients that underwent OLT between 2002 and 2010 with known CAD. Records were reviewed and patterns of BB (uninterrupted therapy, interrupted therapy no therapy, at hospital discharge) and statin (preoperative, at hospital discharge) use were categorized as indicated. Chi-square, Fisher's exact test, and ANOVA were employed to compare patterns of use with Length of Stay (LOS), as well as the incidence of death, Myocardial Infarction (MI), and composite death and Myocardial Infarction (MI) at both 30 days and 12 months post-OLT.

Results: Thirty-three patients (73%) were on a BB at admission, and of these 20 (61%) had BB therapy withheld for > 48 hours. Twenty-seven (60%) patients were discharged on a BB. Eight patients out of 45 (18%) were on statin therapy chronically and had the drug continued till the time of OLT. Following transplantation, 1 patient (2%) was discharged on a statin. Overall there were 5 (11%) in-hospital MI in the cohort. Of these, none occurred in patients given continuous BB therapy, while 4 occurred in patients that had BB therapy withdrawn ($p = 0.118$) and 1 in a patient never administered BB. On univariate analysis, mean LOS differed with respect to BB use and was longer in those that had interrupted (20.3 ± 13.9 days) compared with uninterrupted BB therapy (11.5 ± 7.1 ; $p = 0.020$). Composite 1-year mortality and MI was 22% and did not differ with regard to BB or statin prescription at the time of discharge.

Conclusions: In patients with CAD undergoing OLT there is a high rate of perioperative BB withdrawal. In addition, few patients are on statin therapy at the time of OLT, and most are not administered a statin postoperatively. BB withdrawal in this population was associated with a non-significant increase in 30-day MI and a significant increase in LOS. This observation, from the largest CAD-OLT cohort yet reported, calls for identifying reasons for BB withdrawal and provides support for increased vigilance with respect to BB provision in this population.

Introduction

Patients with End-Stage Liver Disease (ESLD) have a prevalence of Coronary Artery Disease (CAD) up to 27% , exceeding that of the general population [1-4]. Moreover, patients with CAD undergoing Orthotopic Liver Transplantation (OLT) experience worse short and long-term outcomes compared to those without CAD [5-7]. While these prognostic implications may limit transplant eligibility, OLT is still frequently offered to patients with CAD [8].

There are few guidelines that address the perioperative management of cardiovascular risk in this specific population [9,10]. Established guidelines do exist for the perioperative

management of patients with known CAD undergoing intermediate or high-risk noncardiac surgery. These include the continuation of BB and statin therapy throughout the perioperative period in an effort to reduce cardiovascular events [11]. However, the adherence and utility of this practice is unknown in the OLT population, as BB therapy may be initiated primarily due to concern for variceal bleeding and statin therapy may be withheld due to concern for hepatotoxicity.

The present study was undertaken to describe patterns of beta-blocker and statin use among patients with CAD undergoing OLT at a tertiary care hospital. In addition, we sought to evaluate

the impact of perioperative BB and statin use on outcomes following OLT in this population.

Methods

After institutional review board approval and the granting of a waiver of informed consent, we searched the institutional transplant database for patients who underwent OLT at the Hospital of the University of Pennsylvania between 2002 and 2010. This search produced a list of 1,075 patients, which was then cross-referenced to a list of all inpatients and outpatients in the University of Pennsylvania Health System who were billed for an ICD-9 diagnostic code related to CAD between 1998 and 2010. These codes included: "acute myocardial infarction", "other acute and subacute forms of ischemic heart disease", "old myocardial infarction", "angina pectoris", "other forms of chronic ischemic heart disease", "aortocoronary bypass status", and "percutaneous transluminal coronary angioplasty status". This cross-reference yielded 251 patients who had undergone OLT between 2002 and 2010 and had been billed for a diagnosis or related diagnosis of CAD (either before or after OLT). Each of these 251 charts was then manually evaluated to corroborate the existence of known CAD, as defined in Table 1, at the time of the patient's OLT. A total of 47 patients met the criteria for analysis. Two of these patients were excluded because they underwent simultaneous liver and heart transplants, leaving 45 patients included in the study.

These 45 patients additionally had their medical records reviewed for the use of a beta blocker or statin 1) during the 30 days prior to hospitalization for OLT; 2) at the time of admission for OLT; 3) during hospitalization for OLT; 4) at discharge from OLT hospitalization; and 5) following discharge up to 30 days post-transplant. Ordinal variables were created for BB use, including "uninterrupted therapy", "interrupted therapy" (defined in Table 1), "no therapy", and "at hospital discharge", and for statin use, including "preoperative" and "at hospital discharge". Chi-square, Fisher's exact test, and analysis of variance (ANOVA) were employed to compare BB and statin use with the following outcomes: 1) myocardial infarction (MI, as defined in Table 1) at 30 days and 12 months post-OLT, 2) mortality at 30 days and 12 months, 3) composite death and myocardial infarction at 30 days and 12 months, and 4) length of hospital stay (LOS).

Results

Baseline characteristics are listed in Table 2. The cohort predominantly comprised of Caucasian males (91%), with a mean age of 61 years. The most common etiologies for ESLD were viral hepatitis (33%) and non alcoholic steatohepatitis (33%). Thirty-six percent of the patients had a history of coronary artery bypass grafting (CABG), 33% had a history of percutaneous coronary intervention (PCI), 24% had been managed medically with an obstructive lesion, $\geq 50\%$ on coronary angiography, and the remaining 7% had been managed medically with a documented history of myocardial infarction. No patients were allergic to beta-blockers. One patient had charted allergies to atorvastatin and rosuvastatin.

The rates of BB and statin use are listed in Table 3. Thirty-three patients in our cohort (73%) were on a BB at admission,

Table 1: Definitions.

	Definitions
Coronary artery disease	Any one or more of the following: 1) history of ≥ 1 documented MI, 2) history of coronary artery bypass grafting (CABG), 3) history of percutaneous coronary intervention (coronary artery angioplasty with or without stenting), 4) coronary angiography demonstrating ≥ 1 significant lesion causing $\geq 50\%$ stenosis
Myocardial infarction	Detection of rise in serum cardiac biomarkers (troponin T) with any of the following evidence of ischemia: 1) chest pain, 2) ECG ST-T wave changes indicative of ischemia, 3) development of pathologic Q waves on ECG, 4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality ²³

Table 2: Baseline Demographic and Clinical Features.

Mean Age (yrs)	61 $\pm$ 5.9
Men	38 (84%)
Women	7 (16%)
Race	
White	41 (91%)
Black	3 (7%)
Hispanic	0 (0%)
Other	1 (2%)
Etiology of ESLD	
Non alcoholic steatohepatitis	15 (33%)
Viral hepatitis	15 (33%)
Cryptogenic	5 (11%)
Alcoholic	5 (11%)
Other	5 (11%)
Coronary risk factors	
Hypertension	27 (60%)
Diabetes Mellitus	26 (58%)
Current or previous smoker	34 (76%)
Hyperlipidemia	12 (27%)
Evidence of CAD	
CABG	16 (36%)
PCI	15 (33%)
Obstructive lesion $\geq 50\%$ h/o MI without revascularization	11 (24%) 3 (7%)

Continuous variables are expressed as mean $\pm$ standard deviation; nominal variables are expressed as number (%). See text for variable definitions.

and out of these 20 (61%) had BB therapy withheld for > 48 hours during their hospitalization. Twenty-seven (60%) patients were discharged on a BB. Among the patients who were administered a BB postoperatively, the mean time between OLT and start of beta-blockade was 2.4 ± 4.9 days. Eight patients (18%) were on statin therapy chronically and had the drug continued to the time of OLT. Following transplantation, 1 patient (2%) was discharged on a statin.

Tables 4 and 5 display the outcomes of myocardial infarction, death, and hospital length of stay following OLT. In our cohort, 5 patients (11%) experienced an in-hospital MI. Of these, 4 occurred in patients that had BB therapy withdrawn (Figure 1), although this was not a statistically significant difference as compared to patients in whom BB therapy was uninterrupted ($p = 0.118$). Of the 5 patients with in-hospital MI, one was on statin therapy. In total, there were 5 deaths (11%) at 12 months post-transplant, 3 on BB at discharge and none on statin therapy at discharge. Composite 1-year mortality and MI was 22% and did not differ with regard to BB (provided 22%; not provided 22%; $p = 0.637$) or statin prescription (provided 0%; not provided 23%; $p = 0.601$) at the time of discharge (Figure 2).

Lastly, univariate analysis revealed that mean LOS differed with respect to BB use and was longer in those that had interrupted (20.3 ± 13.9 days) compared with uninterrupted BB therapy (11.5 ± 7.1 ; $p = 0.020$) (Figure 3). LOS did not vary between those provided preoperative statins (13.6 days) compared to those that were not (17.0 days; $p = 0.422$).

Discussion

The significant prevalence of CAD in the ESLD population has recently been recognized, and the presence of CAD has been

Table 3: Peri-operative Beta-blocker and Statin use.

	Beta-blocker	Statin
30 days prior to hospital admission for OLT surgery	33 (73%)	8 (18%)
Day of admission to hospital for OLT surgery	28 (62%)	8 (18%)
Immediately pre-anesthesia for OLT surgery	24 (53%)	8 (18%)
Discharge from hospital following OLT	27 (60%)	1 (2%)
30 days following OLT	28 (62%)	2 (4%)

All values are expressed as number (%).

Table 4: 30 days Outcomes and Peri-operative BB and Statin Therapy.

	All n = 45	BB Withdrawn		p value	Perioperative Statin		p value
		Yes (n = 20)	No (n = 13)		Yes (n = 8)	No (n = 37)	
Death	0	0	0		0	0	
MI	5 (11%)	4 (20%)	0	0.12	1 (13%)	4 (11%)	0.64
LOS	16.4 ± 11.6	20.3 ± 13.9	11.5 ± 7.1	0.02	13.6 ± 9.3	17.0 ± 12.1	0.42

Continuous variables are expressed as mean ± standard deviation; nominal variables are expressed as number (%). See text for variable definitions.

Table 5: 12 months Outcomes and Peri-operative BB and Statin Therapy.

	Total	Discharge BB		p value
		Yes	No	
	(n = 45)	(n = 27)	(n = 18)	
Death	5 (11.1%)	3 (11.1%)	2 (11.1%)	0.68
MI	6 (13.3%)	4 (14.8%)	2 (11.1%)	0.54
Composite Death and MI	10 (22.2%)	6 (22.2%)	4 (22.2%)	0.64

All values are expressed as number (%).

Rate of 30-day MI vs. perioperative BB therapy

Figure 1: Rate of 30-day MI vs. perioperative BB therapy.

Rate of 12-month MI/death vs. BB prescription at discharge

Figure 2: Rate of 12-month MI/death vs. BB prescription at discharge.

LOS vs. perioperative BB use

Figure 3: LOS vs. perioperative BB use.

demonstrated to predict poor outcomes in patients undergoing OLT. Three-year mortality rates in this population have been reported as high as 50%, with half of the deaths occurring in the first 35 days after transplant [5]. In addition, cohort studies by Deidrich et al. [6] and Yong et al. [7] have established that this population fares reliably worse than those without known CAD. The present study identified high 1 year-mortality (11%), MI

(13%), and composite mortality/MI (22%) rates, similar to those identified in the aforementioned cohorts.

Management of perioperative cardiovascular risk in this population might include the provision of BB and statin drugs – the continuation of which is recommended in an effort to reduce cardiovascular events and mortality in those with CAD undergoing high risk surgeries [11-16]. We identified a high rate of perioperative BB withdrawal – for which there are several potential explanations. At baseline, patients with cirrhosis are peripherally vasodilated and have low systemic vascular resistance, [17] and hypotension is often more pronounced around the time of transplant due to complicating occurrences (e.g. hemorrhage, sepsis), or the sudden hemodynamic changes that accompany liver transplantation [18]. An alternative explanation for frequent perioperative BB withdrawal is that many OLT candidates might have been initiated on chronic nonselective BB therapy for variceal bleeding prophylaxis, rather than for cardiac indications. Since acquisition of a healthy liver mitigates the risks of variceal bleeding, patients on nonselective beta-blockers prior to transplant may have these drugs discontinued perioperatively despite having CAD as an indication for continuation.

Importantly, we observed a trend toward increased 30-day MI and a statistically significant increase in hospital LOS among those with BB withdrawal. In a retrospective study of 403 patients (with and without CAD) undergoing OLT, BB use was associated with reduced 30-day mortality and reduced 30-day death and myocardial infarction [8]. Whether or not the LOS or trend toward increased MI in the present investigation are related to BB withdrawal, or representative of interceding co-morbidities is unclear but warrants further investigation in a prospective fashion.

Regarding statin therapy, few patients were on a statin at the time of OLT, most were not administered a statin postoperatively, and there was no relationship between statin therapy and outcomes. We speculate that common concerns regarding statin use in the OLT community may include 1) statin-associated transaminitis following OLT complicating the detection of acute rejection, and 2) fear of potential hepatotoxicity associated with statin use. Results from studies in patients with elevated liver enzyme levels, non alcoholic fatty liver disease, hepatitis C, and cirrhosis have shown benefit of statin therapy without increased risk of adverse effects [19]. In addition, between 16% and 43% of liver transplant recipients have increased plasma cholesterol levels (in part due to their immunosuppressive regimens), [20,21] and achievement of therapeutic goals among OLT patients is attainable with a low incidence of adverse events [22]. Thus, while the theoretical risk of confusing a statin-associated rise in liver enzymes with acute rejection remains a concern in patients with CAD undergoing OLT, prospective trials are needed to weigh the risk/benefit of statin administration in this setting.

To our knowledge, the present study represents the largest reported cohort of patients with CAD who underwent OLT, and the only one that describes patterns of BB and statin use in this population, along with associated outcomes. However, the present study has limitations: it is retrospective and single center. Moreover, although significant with respect to patterns of statin

use, the number of patients on statin therapy in this population was low, precluding meaningful conclusions regarding outcomes.

Whether perioperative beta-blockers and statins improve outcomes in patients with CAD undergoing liver transplantation is unknown. Our study suggests a protective effect of continuing BB therapy perioperatively in those already taking a BB, but our results may be confounded by the medical complications of transplant that might necessitate interruption of BB therapy. Nonetheless, our observations call for identifying reasons for BB withdrawal and provide support for increased vigilance with respect to BB provision in this population. Prospective trials are needed to elucidate the impact of both beta-blockers and statins on CAD patients undergoing OLT. If these therapies are shown to be advantageous, then patients who have historically been excluded from consideration may eventually benefit from this lifesaving surgery.

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