Rev Bras Anestesiol. 2015;65(3):170–176

REVISTA BRASILEIRA DE ANESTESIOLOGIA

Official Publication of the Brazilian Society of Anesthesiology
www.sba.com.br

SCIENTIFIC ARTICLE

Influence of preoperative propranolol on cardiac index during the anhepatic phase of liver transplantation

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Received 3 November 2013; accepted 5 February 2014
Available online 20 February 2015

KEYWORDS
Liver transplant;
Cardiac output;
Beta-adrenergic antagonist;
Propranolol

Abstract
Introduction: Liver transplantation is the best therapeutic option for end-stage liver disease. Non-selective beta-blocker medications such as propranolol act directly on the cardiovascular system and are often used in the prevention of gastrointestinal bleeding resulting from HP. The effects of propranolol on cardiovascular system of cirrhotic patients during liver transplantation are not known.
Objective: Evaluate the influence of propranolol used preoperatively on cardiac index during the anhepatic phase of liver transplantation.
Method: 101 adult patients (73 male [72.2%]) who underwent cadaveric donor orthotopic liver transplantation by piggyback technique with preservation of the retrohepatic inferior vena cava performed at Hospital das Clinicas, Federal University of Minas Gerais were evaluated. There was no difference in severity between groups by the MELD system, $p = 0.70$. The preoperative use of propranolol and the cardiac index outcome were compared during the anhepatic phase of liver transplantation in 5 groups (I: increased cardiac index, II: cardiac index reduction lower than 16%, III: cardiac index reduction equal to or greater than 16% and less than 31%, IV: cardiac index reduction equal to or greater than 31% and less than 46%, V: cardiac index reduction equal to or greater than 46%).
Results: Patients in group I (46.4%) who received propranolol preoperatively were statistically similar to groups II (60%), III (72.7%), IV (50%) and V (30.8%), $p = 0.57$.
Conclusion: The use of propranolol before transplantation as prophylaxis for gastrointestinal bleeding may be considered safe, as it was not associated with worsening of cardiac index in anhepatic phase of liver transplantation.

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http://dx.doi.org/10.1016/j.bjane.2014.02.017

PALAVRAS-CHAVE
Transplante de fígado;
Débito cardíaco;
Antagonista adrenérgico beta;
Propranolol

Influência do propranolol pré-operatório no índice cardíaco durante a fase anepática do transplante hepático

Resumo
Introdução: O transplante hepático (TH) é a melhor opção terapêutica para doença hepática em estágio terminal (DHET). As medicações betabloqueadoras não seletivas, como o propranolol, atuam diretamente no sistema cardiovascular (SCV) e são frequentemente usadas na prevenção de hemorragia digestiva decorrente da HP. Os efeitos do propranolol no SCV de cirróticos durante o TH não são conhecidos.
Objetivo: Avaliar a influência do uso pré-operatório do propranolol no índice cardíaco (IC) durante a fase anepática do TH.
Método: Avaliaram-se 101 pacientes adultos (73 homens, 72,2%) submetidos a transplante ortotópico de fígado doador cadáver, pela técnica de *piggyback* com preservação da veia cava inferior retro-hepática, feito no Hospital das Clínicas da Universidade Federal de Minas Gerais. Não houve diferença de gravidade pelo sistema MELD entre os grupos, p = 0,70. Foram comparados o uso pré-operatório de propranolol com o desfecho do IC durante a fase anepática do TH em cinco grupos (I: aumento do IC; II: redução do IC inferior a 16%; III: redução do IC igual a ou maior do que 16% e menor do que 31%; IV: redução do IC igual a ou maior do que 31% e menor do que 46%; V: redução do IC igual a ou maior do que 46%).
Resultados: Pacientes que fizeram uso pré-operatório de propranolol no grupo I (46,4%) foram estatisticamente semelhantes aos dos grupos II (60%), III (72,7%), IV (50%) e V (30,8%), p = 0,57.
Conclusão: O propranolol no pré-transplante, como profilaxia para hemorragia digestiva, pode ser considerado seguro, pois não se associou à pioria do IC na fase anepática do TH.

Introduction

Since the first liver transplantation (LT) performed in humans by Starzl in Denver, USA, in 1963, major advances such as better preservation of organs, improvement of surgical techniques, better knowledge of anesthesiology, and immunosuppressive therapy evolution have made liver transplantation the best treatment option for end-stage liver disease (ESLD).[1] Currently, post-LT survival is approximately 90%, 85% and 80% at 1, 3 and 5 years, respectively.[2]

Cirrhosis is the most common cause of portal hypertension (PH) and causes increase in both intrahepatic vascular resistance and portal flow. PH is associated with serious complications, such as ascites, hepatic encephalopathy, and bleeding from esophagogastric varices.[3] The hepatic venous pressure gradient (HVPG) reduction below 12 mmHg is essential to minimize the risk of upper gastrointestinal bleeding in patients with PH. Non-selective beta-blockers drugs, such as propranolol and pindolol, reduce PH by decreasing the cardiac output (CO) and splanchnic vasoconstriction and, thus, the portal blood flow.[3–5] The pharmacological effects of beta-blockers interfere with the cardiovascular system (CVS) during the perioperative period of LT and affect the transplanted liver functionality.[6]

LT intraoperative period is classically divided into three phases: pre-anhepatic, anhepatic, and neohepatic. During the anhepatic phase, severe hemodynamic changes may occur and it is important that the anesthesiologist be prepared to optimize this patient during graft reperfusion, a critical time with a high incidence of CVS instability.[7]

Thus, it is important to know the effects of preoperative propranolol during LT.

Objectives

Evaluate the effect of preoperative use of propranolol and CI clinical and surgical variables during the anhepatic phase of orthotopic transplantation of cadaver donor orthotopic liver transplantation.

Method

Prospective study was performed at the Gastroenterology Alfa Institute of the Hospital das Clinicas, Federal University of Minas Gerais (HC-UFMG). This research was approved by the Research Ethics Committee of UFMG, CAAE 0244.0.203.000-08 and CAAE 0406.0.203.000-11 projects.

During the study period, from August 29, 2008 to January 5, 2012, 218 liver transplants were performed, wherein 13 of them are of retransplantation. A total of 114 patients, who agreed with and signed the informed consent after the invitation to participate, met the inclusion criteria. Thirteen patients were excluded because of hemodynamic data collection failure.

Inclusion criteria were age $\geq$18 years, transplantation with cadaver donor by piggyback technique, and signing the informed consent. Exclusion criteria were previous LT and hepatectomy, preoperative hemodynamic instability

characterized by the need for vasopressor agents, acute liver failure, and autoimmune hepatitis.

One hundred and one patients participated in the study, 73 male (72.2%). LT indications were: post-viral C cirrhosis (33.7%), ethanol cirrhosis (28.7%), cryptogenic cirrhosis (20.8%), post-viral B cirrhosis (6.9%), primary biliary cirrhosis (3.9%), and others (5.9%). Fifty-four patients were receiving beta-blockers in the pretransplant period (53.5%), and propranolol was the drug used for prophylaxis of gastroesophageal varices bleeding.[3]

The study patients underwent balanced general anesthesia. Anesthesia was induced with etomidate ($0.3\,mg\,kg^{-1}$), fentanyl ($5\,\mu g\,kg^{-1}$), and rocuronium ($1.2\,mg\,kg^{-1}$), maintained with isoflurane (1 MAC), and monitored by the anesthetic gas analyzer. Additional doses of rocuronium and fentanyl were used as needed.

Before surgical incision, all patients underwent the following monitoring: intra-arterial pressure by radial artery catheterization, pulmonary artery pressures, pulmonary artery occlusion pressure, and continuous cardiac output using the Swan-Ganz DDC-Edwards® catheter and Vigilance-Edwards® monitor. Data included intra-arterial mean pressure (IAP), central venous pressure (CVP), mean pulmonary artery pressure (PAP), pulmonary capillary pressure (PCP), heart rate (HR), and cardiac output (CO). In addition to the hemodynamic data the dosage of vasopressor drugs used in intraoperative was recorded.

Measurements were performed at the following times: induction of anesthesia (T1); beginning of anhepatic phase characterized as the portal vein clamping (T2); 5 min before graft reperfusion, characterized as the end of anhepatic phase (T3). In this study the time between T2 and T3 was considered the anhepatic phase duration.

From collected data, the body surface area (BSA), peripheral vascular resistance index (PVRI), and CI were calculated using the Vigilance-Edwards® monitor. Body mass index (BMI) was calculated using the following formula: BMI = weight (kg) $\times$ height $(m)^{-2}$. The Meld (model for end-stage liver disease) used in this study was the calculated and not the corrected Meld.

According to the percentage change in CI, occurring between the beginning (T2) and the end (T3) of the anhepatic phase, and the severity of myocardial impairment function, the patients' results were divided into five groups: Group I: increased CI; Group II: CI reduction lower than 16%; Group III: CI reduction equal to or greater than 16% and less than 31%; Group IV: CI reduction equal to or greater than 31% and less than 46%; and Group V: CI reduction equal to or greater than 46%). Groups II, III, IV, and V had an unfavorable outcome of cardiac index.

Statistical analysis

SPSS version 18 was the software used in the analysis. The reference level of significance in univariate analysis was 0.20. In the multivariate analysis, a 0.05 significance level was considered.

Shapiro–Wilk normality test was used for continuous variables in order to decide for parametric or non-parametric tests in data analysis.

Table 1 Descriptive analysis of patients' variables.

Variables	($n = 101$) Mean (±SD)
Meld	18.07 (±5.64)
Age	50.57 (±10.43)
Weight (kg)	75.43 (±16.49)
Height (m)	168.37 (±9.5)
BMI ($kg\,m^{-2}$)	26.51 (±4.86)
CI T2 ($L\,min^{-1}\,m^{-2}$)	4.2 (±1.6)
SVRI T2 ($dyne\,s\,cm^{-5}\,m^{-2}$)	1276 (±521)
MAPm (mmHg)	67.6 (±16.9)
CVPm (mmHg)	7.8 (±3.4)
Noradrenaline ($mcg\,kg^{-1}\,min^{-1}$)	0.38 (±0.52)
CI T3 ($L\,min^{-1}\,m^{-2}$)	3.50 (±1.56)
SVRI T3 ($dyne\,s\,cm^{-5}\,m^{-2}$)	1668 (±979)
ΔCI (%)	−14.3 (±30.3)
T2/T3 (min)	118.4 (±37.7)

All data are presented as mean (±standard deviation). Meld, model for end-stage liver disease; BMI, body mass index; CI T2, cardiac index at the beginning of anhepatic phase; SVRI T2, systemic vascular resistance index in early anhepatic phase; MAPm, average mean arterial pressure during anhepatic phase; CVPm, mean central venous pressure during anhepatic phase; CI T3, cardiac index at the end of anhepatic phase; SVRI T3, systemic vascular resistance index at the end of anhepatic phase; ΔCI, cardiac index variation between the beginning and end of anhepatic phase; T2/T3, time of anhepatic phase.

In the descriptive analysis, continuous variables were expressed as mean values and standard deviations and categorical variables as frequency and percentage.

For comparison of continuous variables in the five independent groups (I, II, III, IV, and V), the mean comparison test ANOVA was used when the variables had normal Gaussian distribution and the Kruskal–Wallis test for median comparison when the variables did not reach Gaussian distribution.

To evaluate the association of categorical variables in the five groups, the linear trend chi-square test was used because in this case the groups have an importance of ordering.

Results

Descriptive analysis of the patients' clinical characteristics is shown in Table 1.

Table 2 shows the frequency and percentage of some categorical variables.

Table 3 shows the association between categorical variables and CI variation in the different groups.

Table 4 shows the association between continuous variables with CI variation in different groups.

Discussion

Since the development of propranolol by James Black[8] for more than four decades, the adrenergic beta-blockers have been used for treatment of hypertension, coronary artery disease, myocardial infarction, and heart failure, standing

Table 2 Characteristic of study population in frequency and percentage.

Variable	($n = 101$)
Sex (male)	73 (72.3%)
Hepatocellular carcinoma (yes)	22 (21.8%)
Preoperative beta-blocker (yes)	54 (53.5%)
Noradrenaline T3 (yes)	65 (64.4%)
Temporary portocaval anastomosis (yes)	16 (15.8%)
Groups	
I	28 (27.7%)
II	20 (19.8%)
III	22 (21.8%)
IV	18 (17.8%)
V	13 (12.9%)

All data are presented in frequency (percentage). T3, end of anhepatic phase.

out mainly by the action on beta-adrenergic receptors in the CVS. In the heart, beta-1 receptors are present in the sinoatrial node (speeding depolarization), cardiac muscle (increasing contractility), and transmission tissue (increasing conduction velocity) and determine increase in cardiac output. Beta-2 receptors act on the peripheral vascular muscle (causing vasodilation).[9] In drug prevention of upper gastrointestinal bleeding by esophagogastric varices in patients with PH, the beta-blocker is indicated at low initial doses (propranolol 20 mg day^{-1}) with a progressive increase according to patient tolerance and HR reduction.[10]

Systolic ventricular function is determined by preload, afterload, and myocardial contractility — factors that affect the CI. During preoperative evaluation of ESLD patients CVS should be considered because terminal liver disease may be associated with cirrhotic cardiomyopathy. In these patients, CO might be increased due to reduced afterload even in the presence of contractile dysfunction. However, when the CVS is highly demanded as during LT the myocardial dysfunction may manifest and cardiac response may be unsatisfactory and determine an unfavorable outcome.[11] Wong et al., evaluating myocardial function of asymptomatic cirrhotic patients for cardiovascular disease during exercise found a smaller increase in CO compared with control. The decrease in cardiac performance has as factors left ventricular hypertrophy, diastolic dysfunction, and reduced chronotropic response.[12] In this study, we evaluated the CI variation during LT anhepatic phase which is a very demanding period for the CVS, in order to find preoperative factors that may be associated with an unfavorable outcome, which is the worsening of myocardial performance.

The classical technique of LT involves the donor hepatectomy with retrohepatic vena cava resection associated with temporary occlusion of the portal and cava veins during the anhepatic phase, which causes decreased venous return to the heart, decreased renal perfusion, and congestion of the splanchnic venous system in this phase.[13] During the surgical procedure, to avoid interference of the technique used on the analyzed data, we included only the LT performed with the piggyback technique, in which there is preservation of the inferior vena cava. Even with the piggyback technique, the portal vein needs to be occluded causing increased portal pressure with splanchnic bed congestion and intestinal edema. In 1993, Tzakis et al. described the use of piggyback technique with the placement of temporary portocaval shunt (TPCS) for portal vein communication with the infrahepatic inferior vena cava during the anhepatic phase.[14] Figueras et al., in order to assess whether TPCS would improve the hemodynamic and metabolic evolution during LT with piggyback technique, found an improved hemodynamic profile with less need for blood products in TPCS group, but this benefit was more evident in a subgroup of patients with portal flow exceeding 1000 mL min^{-1} or portocaval gradient greater than or equal to 16 mmHg.[13] Margarit et al.[15] evaluated the advantages of TPCS during LT and concluded that TPCS during the anhepatic phase reduces the need for packed red blood cell transfusion and improves postoperative renal function, only in patients with portal vein flow exceeding 800 mL min^{-1}. Muscari et al.,[16] evaluating 84 patients undergoing LT with the piggyback technique, concluded that the routine use of TPCS is not justified. In the present study, TPCS was performed during the anhepatic phase in only 15.8% of patients (Table 2), and there was no association between TPCS and percentage change in CI during anhepatic phase (Table 3).

Table 4 shows that some moderating variables that could influence the outcome were controlled. Important factors in this evaluation were the duration of anhepatic phase (T2/T3), which could be increased by surgical difficulty.

Table 3 Association of categorical variables with the five groups of cardiac index variation in the anhepatic phase.

	Groups ($n = 101$)					p
	I ($n = 28$)	II ($n = 20$)	III ($n = 22$)	IV ($n = 18$)	V ($n = 13$)	
Sex (male)	21 (75)	13 (65)	15 (68.2)	13 (72.2)	11 (84.6)	0.616
Hepatocellular carcinoma (yes)	5 (17.9)	4 (20)	5 (22.7)	4 (22.2)	4 (30.8)	0.387
Beta-blocker (yes)	13 (46.4)	12 (60)	16 (72.7)	9 (50)	4 (30.8)	0.575
Noradrenaline T3 (yes)	19 (67.9)	12 (60)	15 (68.2)	9 (50)	10 (76)	0.951
Temporary portocaval anastomosis (yes)[a]	2 (7.1)	2 (10)	6 (27.3)	3 (16.7)	3 (23.1)	0.292

All data are presented in frequency (percentage). T3, end of anhepatic phase; beta-blocker, preoperative use. Chi-square test for linear trend.

[a] Fisher's exact attest.

Table 4 Association of continuous variables with the five groups of cardiac index variation in the anhepatic phase.

	Group ($n = 101$)					p
	I ($n = 28$)	II ($n = 20$)	III ($n = 22$)	IV ($n = 18$)	v ($n = 13$)	
Meld	18.7 (8.5–40.6)	16.5 (6.4–24.3)	17.8 (6.4–26.2)	17.8 (7.8–30.4)	20.0 (7.8–34.1)	0.701
Age (years)	50.8 (29.5–67.2)	51.5 (20.3–66.0)	51.6 (31.8–62.7)	55.1 (18.8–66.6)	46.3 (29.4–66.9)	0.281
Weight (kg)	78.5 (55–105)	79.9 (48–103)	73 (45.8–93)	70 (52.5–133.5)	76 (47–113)	0.784
Height (cm)[a]	168.7 (±8.2)	165.85 (±9.0)	166.62 (±10.8)	170.39 (±9.7)	171.92 (±10.2)	0.335
BMI ($kg\,m^{-2}$)	27.2 (18.7–34.1)	27.1 (19.1–36.3)	25.9 (19.3–30.3)	25.0 (19.5–45.9)	27.4 (19.6–34.1)	0.552
CVPm (mmHg)[a]	8.3 (±3.3)	8.8 (±3.4)	7.1 (±3.7)	6.9 (±2.9)	7.6 (±3.1)	0.314
MAPm (mmHg)	69 (40–105)	74 (41–115)	61 (40–133)	65 (36–100)	57 (41–117)	0.211
T2/T3 (min)[a]	117.9 (±41.5)	128.0 (±35.7)	109.6 (±35.7)	127.61 (±41.6)	107.15 (28.1)	0.319

Meld, model for end-stage liver disease; BMI, body mass index; CVPm, mean central venous pressure during anhepatic phase; MAPm, average mean arterial pressure during anhepatic phase; T2/T3, duration of anhepatic phase. Data are presented as median (minimum-maximum) Kruskal–Wallis test, except the data.

[a] presented as mean (±standard deviation) ANOVA-test.

The CVPm, which could be influenced by partial clamping of vena cava with the piggyback surgical technique and influence CI, was statistically similar in all groups evaluated. Raval et al., in a review article, reported that ESLD patients with compromised systolic and diastolic function not observed at rest, but during periods of high demand, which reduces the CI by compromising the contractile function, diastolic relaxation, and myocardial electrophysiological conduction. These changes in cirrhotic patients are known as cirrhotic cardiomyopathy and are directly related to the ESLD severity.[17] In our study, based on Meld system, all groups were statistically similar and showed that there was no interference of the liver disease severity on CI.

In a review article of the pathophysiology and clinical implications of cirrhotic cardiomyopathy, Yang and Lin reported the importance of beta-adrenergic receptors for heart contractile function and the involvement of these receptors in ESLD patients.[18] Zenghua et al., in an experimental study, concluded that myocardial contractility in response to beta-adrenergic receptor stimulation was attenuated in cirrhotic rats due to decreased density associated with the signaling pathway involvement of these receptors.[19] Villas-Boas et al., studying the effects of propranolol on renin-angiotensin system in cirrhotic patients, reported changes in hemodynamic parameters with reduced CI in LT pre-anhepatic phase in patients treated with propranolol preoperatively.[20] Aiming at evaluating the effect of propranolol on myocardial function during the anhepatic phase, we correlated the patients receiving propranolol with CI change during the anhepatic phase and found no statistically significant association (Table 3). The propranolol dose of our patients ranged from 20 mg to 120 mg day. The clinical condition of ESLD patients rarely allows improved administration of the adrenergic beta-blocker medication.[10] Non-interference of propranolol on CI variation may be due to the preoperative dose be considered low, so there is significant beta-adrenergic receptor blockade in the heart and myocardial contractile function impairment in this moment of myocardial stress, which is the anhepatic phase.

We believe that myocardial depression during the anhepatic phase may occur due to pro-inflammatory cytokine accumulation,[21] occurred during the LT and intensified at the end of this phase, associated with latent cirrhotic cardiomyopathy. This association between inflammatory cytokine and worsening of myocardial performance has been studied in septic shock,[22,23] which can bring substrate for a future understanding of this event in LT.

Conclusion

The use of propranolol in cirrhotic liver pre-transplantation for prophylaxis of bleeding by esophagogastric varices is safe for CVS during the anhepatic phase of liver transplantation.

Conflicts of interest

The authors declare no conflicts of interest.

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