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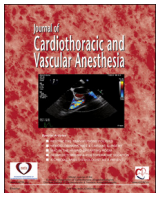

ORIGINAL ARTICLE

Relationship Between Intraoperative Hypotension and Acute Kidney Injury After Living Donor Liver Transplantation: A Retrospective Analysis

Toshiyuki Mizota, MD, PhD*, Miho Hamada, MD, Shino Matsukawa, MD, Hideya Seo, MD, Tomoharu Tanaka, MD, PhD, Hajime Segawa, MD, PhD

Department of Anesthesia, Kyoto University Hospital, Kyoto, Japan

Objective: Acute kidney injury (AKI) is common after liver transplantation (LT) and has a significant impact on outcomes. Although several risk factors for post-LT AKI have been identified, the effect of intraoperative hemodynamic status on post-LT AKI remains unknown. Therefore, the authors aimed to investigate the relationship between hemodynamic parameters during LT and postoperative AKI.
Design: A retrospective observational study.
Setting: University hospital.
Participants: Patients who underwent living donor LT (n = 231).
Interventions: None.
Measurements and Main Results: Severe AKI (stages 2-3 according to recent guidelines) was the primary outcome. Multivariable logistic regression analysis was used to control for confounding variables to obtain the independent relationship between intraoperative hemodynamic parameters (mean arterial pressure [MAP] and cardiac index) and severe AKI. The prevalence of severe AKI was 30.7%. Nadir MAP during the surgery was independently predictive of severe AKI (adjusted odds ratio, 2.11 [95% confidence interval, 1.32-3.47] per 10-mmHg decrease; p = 0.002). Subgroup analyses based on various patient or operative variables and extensive sensitivity analyses showed substantially similar results. Severe hypotension (MAP < 40 mmHg), even for fewer than 10 minutes, was related significantly to severe AKI (adjusted odds ratio, 3.80 [95% confidence interval, 1.17-12.30]; p = 0.026). In contrast, nadir cardiac index was not related significantly to severe AKI.
Conclusions: The authors found an independent relationship between degree of intraoperative hypotension and risk of severe AKI in living donor LT recipients. Severe hypotension, even for a short duration, was related significantly to severe AKI.

Key Words: acute kidney injury; hypotension; liver transplantation; living donors; outcomes; risk factors

ACUTE KIDNEY INJURY (AKI) occurs in 33% to 78% of patients undergoing liver transplantation (LT) and has a significant impact on patient and graft outcomes.[1-3] Previous studies have identified several patient- and procedure-related risk factors for post-LT AKI including female sex,[3] obesity,[3,4] preoperative chronic kidney disease (CKD),[5,6] diabetes mellitus,[1,7,8] high model for end-stage liver disease (MELD) score,[4,8-12] preoperative hypoalbuminemia,[4,13] large amount of blood loss,[6,9,14] and overexposure to calcineurin inhibitors (CNIs).[8,15-18] Moreover, small-for-size graft is known as a living donor LT (LDLT)-specific risk factor for AKI.[4,8]

However, most of these studies did not evaluate intraoperative hemodynamic variables (eg, blood pressure and cardiac

Address reprint requests to Toshiyuki Mizota, MD, PhD, Department of Anesthesia, Kyoto University Hospital, 54 Shogoin-Kawahara-Cho, Sakyo-Ku, Kyoto606-8507, Japan.
E-mail address: mizota@kuhp.kyoto-u.ac.jp (T. Mizota).

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output), and data addressing the association between hemodynamic status during LT and postoperative AKI are lacking.

The authors therefore aimed to investigate the relationship between hemodynamic parameters during LT and development of postoperative AKI. Specifically, the hypothesis that the degree of hypotension during LT is related to a higher risk of AKI was tested.

Methods

The ethics committee of Kyoto University Hospital approved this single-center retrospective study (approval number: R0275, 2 November, 2015) and waived the requirement for informed consent. Patients aged 18 years or older who underwent LDLT at Kyoto University Hospital from March 2008 to April 2015 were included. Patients with fulminant hepatic failure, defined as the development of encephalopathy within 8 weeks of the onset of symptoms, were excluded. In addition, patients who had end-stage renal disease (ie, estimated glomerular filtration rate of < 15 mL/min/1.73 m^2, as determined using a formula validated in Japan: estimated glomerular filtration rate $= 194 \times [\text{serum creatinine}]^{-1.094} \times \text{age}^{-0.287}$ [$\times 0.739$ for females][19] or receipt of long-term hemodialysis) preoperatively also were excluded because AKI assessment was no longer relevant.

Perioperative Management

At the authors' institution, anesthetic drugs used for LDLT are standardized; anesthesia was induced using propofol (1-1.5 mg/kg) and remifentanil (0.1 μg/kg/min) and maintained using sevoflurane (1%-1.5%) and remifentanil (0.1-0.3 μg/kg/min). Red blood cell concentrate transfusion during the surgery was aimed at maintaining a hematocrit concentration of 25% to 30%. Although the use of vasopressor was left to the responsible anesthesiologist, the first-line vasopressor during the surgery was phenylephrine. If phenylephrine was ineffective, dopamine, norepinephrine, vasopressin, or epinephrine was considered.

Immunosuppression was provided according to the institutional protocol as previously described.[20] The basic immunosuppressive regimen comprised a CNI (tacrolimus or cyclosporine) and low-dose corticosteroids. Additionally, recipients of blood-type-incompatible liver grafts had preoperative anti-CD20 antibody (rituximab, 375 mg/m^2) with preoperative plasma exchange, postoperative hepatic artery infusion of prostaglandin E1 (0.01 μg/kg/min) and methylprednisolone (125 mg/day), and postoperative cyclophosphamide (2 mg/kg/day), followed by mycophenolate mofetil (starting dose, 500 mg/day; maintenance dose, 1,000 mg/day).

Intraoperative Hemodynamic Parameters

All patients had invasive arterial monitoring and pulmonary artery catheters (CCOmbo Continuous Cardiac Output Catheter with SvO_2 and EDV, Edwards Lifesciences, CA) during the surgery. The mean arterial pressure (MAP) and cardiac index (CI) during the surgery were recorded automatically every minute directly into an anesthesia information management system (Nihon Kohden, Tokyo, Japan). The raw MAP values were filtered manually to purge artifacts due to disconnections during blood sampling or flushing of the arterial line: MAPs of < 20 or > 150 mmHg were considered as artifacts, and the last nonartifact MAP was carried forward. For CI, such manual filtering was not conducted and raw data were used for analysis. For each patient, nadir MAP, nadir CI, relative decreases of MAP and CI from baseline, and number of minutes spent with an MAP of < 40 and 50 mmHg were calculated. Baseline values for MAP were defined as the median MAP of all blood pressure measurements recorded in the medical chart within 3 days preoperatively. Baseline values for CI were defined as the CI values obtained 5 minutes before the start of the surgery; if CI monitoring was initiated after the start of the surgery, the CI value obtained 1 hour after the start of the surgery was considered as the baseline value. In addition, to determine the timing of the onset of hypotension, the case was divided into 5 surgical events: (1) induction, before the start of surgery; (2) preanhepatic, from the start of surgery to removal of the native liver; (3) anhepatic, from removal of the native liver to graft reperfusion; (4) postreperfusion, from 0-to-30 minutes after graft reperfusion; and (5) neohepatic, from 30 minutes after graft reperfusion until leaving the operating room. The nadir MAP during each surgical event was extracted.

Other Exposures

The following patient and perioperative variables were obtained from patients' medical records: patient characteristics, preoperative serum albumin and creatinine (SCr) concentrations, MELD score, graft-recipient weight ratio, duration of surgery, intraoperative blood loss, amount of blood products used intraoperatively, and CNI overexposure. MELD score was determined through the following equation: $\text{MELD} = 9.57 \times \log_e$ creatinine mg/dL $+ 3.78 \times \log_e$ bilirubin mg/dL $+ 11.20 \times \log_e$ INR $+ 6.43$.[21] Preoperative CKD was defined as an estimated glomerular filtration rate of < 60 mL/min/1.73m^2, as determined using a formula validated in Japan.[19] Averaged CNI trough level within 7 days postoperatively was calculated, and CNI overexposure was defined as averaged trough level of > 10 ng/mL for tacrolimus or > 200 ng/mL for cyclosporine.[8]

Outcome

The primary outcome was severe AKI, defined as stage 2-3 AKI according to the guidelines of Kidney Disease Improving Global Outcomes (a 100% increase in SCr from the baseline or urine output of < 0.5 mL/kg/h for ≥ 12 hours during the first 7 postoperative days).[22] The authors previous study revealed that these stages of AKI were associated independently with an increase in hospital mortality.[20] AKI stages were assigned based on SCr measured daily within 7 days of surgery and urine output measured every 2 hours during postoperative

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