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Vasopressin Use During Liver Transplantation Is Not Associated with Severe Acute Kidney Injury: A Propensity Score Adjusted Regression Analysis

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We use this protocol and it's working

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Abstract

Acute kidney injury is a common complication after liver transplantation. Acute kidney injury occurrence in this population determines higher mortality, increased graft loss, longer hospital and intensive care unit stays, and more progression to chronic kidney disease.
Hemodynamic derangements are treated intraoperatively with vasopressor medications to uphold a mean arterial pressure within the autoregulatory range of the kidney, but the impact of their use, as well as the choice of medication, on postoperative kidney function, is relatively unknown. Vasopressin acts as a portal flow modulator, has a potential catecholamine-sparing effect, and provides benefits for kidney function during distributive shock.
The investigators hypothesized that the intraoperative use of vasopressin could reduce the incidence of postoperative severe acute kidney injury after liver transplantation and planned a retrospective single-center propensity score-adjusted regression analysis to test this hypothesis.

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Vasopressin Use During Liver Transplantation Is Not Associated with Severe Acute Kidney Injury: A Propensity Score Adjusted Regression Analysis - Clinical Research Study Protocol

1 Research Hypothesis

Vasopressin use during liver transplantation reduces postoperative acute kidney injury (AKI).

2 Significance

AKI is a major complication after liver transplantation, with an incidence that exceeds 50%. Liver transplant recipients who develop renal failure experience shorter graft survival, high morbidity and mortality, and an increased incidence of chronic kidney disease, with serious implications. Progression to advanced stages of AKI predicts a worse prognosis[1].
Hemodynamic derangements are treated intraoperatively with vasopressor medications. Vasopressors are administered to uphold a mean arterial pressure within the autoregulatory range of the kidney, but the impact of their use overall, as well as the choice of medication, on postoperative kidney function is relatively unknown.
The use of vasopressin may reduce the necessary dose of catecholamines, thereby limiting adrenoceptor desensitization, preventing sympathetic overactivation, and improving renal function. During distributive shock, vasopressin can increase the glomerular filtration rate[2]. In addition, intraoperative vasopressin was shown to reduce portal and hepatic blood flow in patients undergoing liver surgery, potentially limiting blood loss, and thus possibly mitigating AKI through a separate mechanism[3]. Furthermore, relative vasopressin deficiency has been shown in patients with cirrhosis. Those findings have generated interest in the use of vasopressin as an adjunctive vasopressor agent during liver transplantation. However, the specific role of vasopressor use in this population is not well-defined.

3 Data source:

UCSF Liver Transplant Research group database (June 2012, November 2022).

4 Study Design

Retrospective cohort study

5 Inclusion criteria:

- Age ≥18 years
- Liver transplantation from either:
  a. Donor after neurologic determination of death (DBD)
  b. Living donor
  c. Donor after circulatory death (DCD)

Exclusion criteria:
- Enrollment in a clinical trial at the time of transplantation.
- Simultaneous liver-kidney transplantation.
- Liver transplantation for acute liver failure.
- Graft preservation with machine perfusion.
- Vasopressor administration within 24 hours before transplantation.
- Preoperative intubation.
- Pre- or intraoperative renal replacement therapy (RRT).
- If the patient was retransplanted during the same hospitalization, only the first liver transplantation case will be analyzed.

6 Sampling Strategy

Patients who have received liver transplantation at University of California, San Francisco between June 2012, and November/30th November 2022.

7 Primary exposure/predictor/intervention

Intraoperative vasopressin use, expressed as a binary variable.

8 Primary outcome

Postoperative Severe AKI (stage ≥2), as defined by the International Club of Ascites (ICA) 2015 criteria[4].

Baseline serum creatinine will be defined as the lowest creatinine level within 48 h before surgery. Peak creatinine being the highest creatinine within 48 h after surgery. The stages of AKI will be defined as:
- Stage 1: peak creatinine ≥1.5× baseline creatinine or increase of baseline creatinine by ≥0.3mg/dL;
- Stage 2: peak creatinine >2× baseline creatinine;
- Stage 3: peak creatinine >3× baseline or peak creatinine ≥4.0mg/dL or initiation of RRT within 48 after surgery.

9 Secondary outcomes:
- Stage of AKI at 48h after liver transplantation, defined by ICA 2015 criteria[4];
- AKI requiring RRT at 48 hours after transplant;
- Estimated glomerular filtration rate (eGFR) at 48 hours after transplant, defined by the Chronic Kidney Disease Epidemiology Collaboration (2021 update, without the race factor)[5]:
eGFR (mL/min/1.73 m2) = 141 × min(Scr/κ, 1)α × max(Scr/κ, 1)−1.209 × 0.993Age × 1.018 [if female]; where: Scr is the serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males.
- Alive without need for RRT at one week after transplant;
- Need for RRT at one week after transplant;
- eGFR at one week after transplant;
- Discharged without need for RRT;
- Need for RRT at discharge and mortality at discharge;

- Hospital length of stay;
- Alive without need for RRT at one year after transplant;
- Need for RRT at one year after transplant;
- eGFR at one year after transplant;
- Mortality at one year after transplant.

10 Statistical analysis:

- All analysis will be performed using R software. Continuous variables will be described using medians with interquartile ranges and will be compared by the Wilcoxon rank sum test. Categorical variables will be described using frequencies and percentages, and differences will be assessed using Pearson's chi-squared test or Fisher's exact test. Categorization of continuous covariates, if non-linearity between the covariate and the log odds of the outcome is suspected, will be based on graphical assessment. Cutoff values will be based on either clinical parameters or sample percentiles.
- To ascertain the influence of intraoperative vasopressin administration on liver transplantation recipients postoperative AKI incidence, a propensity score-adjusted multivariate logistic regression will
be conducted to adjust for potential confounding factors. Multiplicative interaction terms will be tested in the regression model between hypotension time and vasopressors administered (intraoperative catecholamine dose and vasopressin use). This model will include perioperative variables we consider potential confounders that might influence both vasopressors use and renal outcomes, outside of the causal pathway, as described in the directed acyclic graph (Figure 1).
- The association between the vasopressin use and the eGFR at one week and at one year after liver transplant will be addressed with a linear multivariable regression model
including the same set of covariates used in the primary model.
- A sensitivity analysis will be performed running the same propensity score- adjusted model on the subpopulation with an intraoperative dose in the top quartile of this cohort.
All tests will be two-sided, alpha - value < 0.05 will be considered statistically significant. No statistical power calculation will be conducted before the study. The sample size will be solely based on the available data.

Propensity Score:

The propensity score adjustment method is a statistical technique for estimating treatment effects in non-randomized studies. In this technique, the propensity score of the treatment – vasopressin use – is included in the final regression model, in addition to treatment status and other covariates. Only covariates measured before exposure will be included for propensity score calculation, to avoid adjusting for mediators. Covariates included in the propensity score calculation model will not be used in the primary model to avoid collinearity. A logistic regression model will be employed to estimate the propensity score (i.e., the probability of receiving treatment):

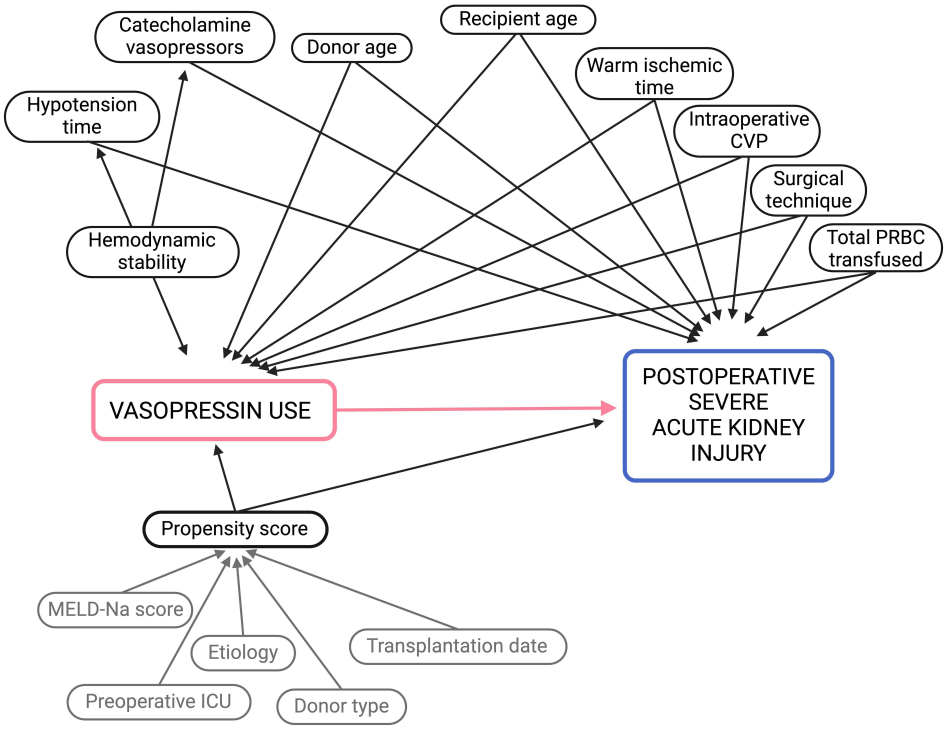
- Donor type (DBD, DCD)
- Transplantation year

- Indication for liver transplantation
- Model for End-stage Liver Disease Sodium (MELD-Na) score
- Preoperative intensive care unit admission

Primary regression model

- Propensity score for vasopressin use
- Donor age
- Recipient age
- Vasopressin use
- Catecholamine vasopressors dose
- Total packed red blood cells transfused
- Warm Ischemic Time (per 10 min)
- Vena cava implantation surgical technique
- Intraoperative central venous pressure
- Hypotension time

10.1 Figure 1: Directed acyclic graph containing variables included in the primary model



11 Intraoperative catecholamine vasopressors total doses administered from surgical procedure start to surgical procedure stop will be considered. Total infusion and boluses dose will be taken into account. Conversion to Norepinephrine Equivalents will be carried out according to ATHOS III trial[6]:

- Norepinephrine will be used as the vasopressor potency reference, in $mcg \cdot kg^{-1} \cdot min^{-1}$.

- Phenylephrine will be converted using a 10:1 ratio (1.0 mcg·kg^{-1}·min^{-1} of phenylephrine = 0.1 mcg·kg^{-1}·min^{-1} of norepinephrine).
- Epinephrine will be converted using a 1:1 ratio (0.1 mcg·kg^{-1}·min^{-1} of epinephrine = 0.1 mcg·kg^{-1}·min^{-1} of norepinephrine).

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