Official Title of the study: Impact of Dexmedetomidine on Acute Kidney Injury Following Living Donor Liver Transplantation: a randomized clinical trial

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Introduction

Acute kidney injury (AKI) is a major complication of liver transplantation (LT) and the incidence of post-operative AKI ranges between 12% and 80%, depending on the definition adopted. There is increasing evidence that post-operative AKI following LT is independently associated with increased costs, recipient and graft outcomes. Although various strategies have been suggested to protect against postoperative AKI after LT, AKI still has a strong impact on the prognosis of LT. The underlying mechanism of postoperative AKI appears to be multifactorial, with numerous preoperative, intraoperative and postoperative factors involved. Among all, hepatic ischemia-reperfusion injury (IRI) and subsequent inflammatory response has been considered as one of main causes of AKI in LT.

Dexmedetomidine (DEX) is a selective α2-agonist and a sedative with anti-inflammatory, analgesic and antioxidant effects. The kidney protective effect of DEX has been highlighted by preventing IRI with decreased systemic inflammatory response and reduced reactive oxygen species. Currently, the effects of DEX on kidney functions has been intensively researched in both animal and human studies. However, the majority of randomized clinical trials with DEX for AKI have been studied in heart surgery and only a limited number of prospective studies have been conducted in that regard in recipients undergoing living donor liver transplantation (LDLT).

In this study, therefore, we evaluated the impact of intraoperative DEX infusion on the incidence of AKI in recipients undergoing LDLT. We also investigated that intraoperative lactate, incidence of delirium, early allograft dysfunction (EAD), duration of mechanical ventilation (MV), intensive care unit (ICU) length of stay (LOS) and hospital LOS.

Study Protocol

Study design and ethical approval

The single-center, double-blinded, randomized controlled study was approved by the institutional review board of the Asan Medical Center (2017-0409) and registered with ClinicalTrials.gov (NCT03522688). The trial was conducted at Asan Medical Center in Seoul, Korea between July 2017 and October 2019. Written consent was obtained from all patients. We collected and analyzed the data in accordance with the ethical standards set in the 1964 Declaration of Helsinki and its amendments.

Participants

Adult recipients scheduled for elective LDLT from July 2017 to October 2019 at Asan Medical Center in Seoul, Korea, were screened for eligibility. Recipients were excluded if they met at least one of the following criteria: recipients with serum creatinine >1.4 mg/dL, any history of chronic kidney disease, dual living donor LT, intraoperative use of veno-veno bypass, left main coronary artery occlusion >50%, hemodynamically significant arrhythmia, left ventricular ejection fraction <50%, use of an α2 agonist to treat hypertension, or a history of severe allergy to drugs. In total, 134 participants were assessed for eligibility and randomly assigned to either the DEX group (n = 67) or control group (n = 67). Four recipients who used veno-venous bypass during the surgery were removed from the study. Finally, 130 participants [DEX (n = 65) and control (n = 65) groups] were analyzed. For randomization, random computer-generated numbers were stored in sealed envelopes that were opened following the induction of anesthesia by an anesthesia nurse who was unaware of the study.

Intervention

DEX (Precedex®, dexmedetomidine hydrochloride, Hospira, Inc., Lake Forest, IL, USA) was continuously infused at a rate of 0.4 μg/kg/h and omission of bolus administration. Infusion of DEX was starting after anesthetic induction and discontinued 2 hours after graft reperfusion. The control group received a same volume of 0.9% saline for the same duration. All interventions were achieved by the anesthetic nurses not responsible for the research.

Primary Outcomes

The primary outcome was incidence of AKI and for that reason the serial assessments of creatinine levels were recorded within the first postoperative week. Postoperative AKI is defined according to the Kidney Disease: Improving Global Outcomes guideline (KDIGO) which described AKI as a change in the serum creatinine from baseline on postoperative days 1–7. The baseline serum creatinine was the concentration measured just before surgery. AKI is defined as an increase in serum creatinine above baseline of ≥0.3 mg/dL within 2 days or ≥50%–99% within 7 days. Once AKI is established, a staging system then divides its severity according to KDIGO criteria. Subgroup analysis was also performed to assess the incidence of AKI by ABO compatibility.

Secondary Outcomes

Serial levels of lactate were collected during the surgical procedure just before the initiation of induction (T0), 1 hour after skin incision (T1), 30min after the removal of the liver (T2), just after reperfusion of the graft (T3), 1 hour after reperfusion (T4) and at end of surgery (T5). Additionally, the maximum level of lactate (Tmax) was evaluated during the postoperative 3 days following LDLT. Incidence of delirium, EAD, and graft failure after 12 months post-LT were also monitored. Finally, duration of MV, ICU LOS and hospital LOS were recorded. The

incidence of delirium between ICU arrival and postoperative day 7 was assessed using the Confusion Assessment Method for the ICU with postoperatively at 12-h intervals or as needed according to the patient's condition. EAD was defined based on postoperative day 7 laboratory values of serum bilirubin higher than 10 mg/dL or INR higher than 1.6. Graft failure was defined as patient death or retransplantation within 1 year. Patients who were alive with a functioning graft 1 year after LT were censored.

Statistical analysis

Data are presented as the mean ± standard deviation, median (interquartile range), or frequency (percentages) unless otherwise stated. Continuous variables were compared using the Student t test or Mann–Whitney U test; categorical variables were compared using the Pearson chi-square test or Fisher exact test, as appropriate. Longitudinally measured outcomes were modeled as a function of time, group and their two-way interaction, using a linear mixed model. The Sidak correction was used to adjust for multiple comparisons. For all analyses, $p<0.05$ was considered statistically significant. SPSS 23 (IBM Corp, Armonk, NY) software was used for all statistical analyses.