Official Title of the study: The Effect of Remote Ischemic Preconditioning in Living Donor Hepatectomy: a randomized clinical trial

NCT number : NCT03386435

IRB approval date: 1th August 2015

Introduction

Liver transplantation(LT) is the gold standard treatment for patients with end-stage liver disease. In light of advancements in surgical techniques, immunosuppressive agents, and perioperative critical care, the overall 3-year survival of patients undergoing LT has exceeded 80%. Despite its outstanding success, LT still entails certain complications including ischemia-reperfusion injury (IRI).

IRI occurs when the blood supply to an organ or tissue is temporarily cut-off and then restored, and it is well-known as an underlying cause of primary non-function, biliary complications, and eventual graft loss after LT. Despite many attempts to ameliorate hepatic IRI, no definitive therapies have been established. In addition, the mechanisms of IRI remain largely unclear.

Remote ischemic preconditioning (RIPC) is a novel and simple therapeutic method to lessen the harmful effects of IRI. RIPC indicate that brief episodes of ischemia with intermittent reperfusion are introduced at a remote site, leading to systemic protection against subsequent insults as evinced on kidney, heart, liver, and other tissues. While RIPC has been shown to reduce hepatic IRI in several small animal studies, the beneficial effects of RIPC in hepatic IRI have been inconsistent. By far, the majority of RIPC studies on hepatic IRI have been animal studies; hence, there are limitations relating to the lack of human clinical trials.

Therefore, our aim was to assess the effects of RIPC on postoperative liver function in living donor hepatectomy.

Study Protocol

Study design and ethical approval

For the donors, the single-center, double-blinded, randomized controlled study was approved by the institutional review board of the Asan Medical Center (2015-0851) and registered with ClinicalTrials.gov (NCT03386435). We collected and analyzed the data in accordance with the ethical standards set in the 1964 Declaration of Helsinki and its amendments.

Participants

For the donor group, adult (aged 18-60 years) liver donors scheduled for elective donor right hepatectomy from August 2016 to July 2017 at Asan Medical Center in Seoul, Korea, were screened for eligibility. Total 160 participants were assessed for eligibility and randomly assigned to either the RIPC group (n=80) or the control group (n=80). 12 donors whose surgical plan changed unexpectedly from open right hepatectomy to other than open right hepatectomy (e.g., laparoscopic right lobectomy [n=9], left lobectomy [n=2], and right posterior segmentectomy [n=1]) were dropped out of the study. The remaining 148 donors (RIPC group [n=75] and control group [n=73]) 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

After induction of anesthesia and before skin incision, we performed RIPC. The protocol involves 3 cycles of 5-minute inflation of a blood pressure cuff to 200 mm Hg to one upper arm, followed by 5-minute reperfusion with the cuff deflated. In the control group, the same maneuver was applied but without cuff inflation. All interventions were performed by the

anesthetic nurses who were not involved in the study.

Outcomes

In donors, plasma concentrations of AST and alanine aminotransferase (ALT) were measured daily during the first postoperative week to assess the extent of hepatocellular damage. The postoperative liver regeneration index (LRI) at postoperative 1 month and the incidence of delayed recovery of hepatic function (DRHF) were used as surrogate parameters indicating the possible benefits of RIPC. The LRI was defined as $[(V_{LR} - V_{FLR})/V_{FLR})] \times 100$, where V_{LR} is the volume of the liver remnant and V_{FLR} is the volume of the future liver remnant. Liver volume was calculated by CT volumetry using 3-mm-thick dynamic CT images. The graft weight was subtracted from the total liver volume to define the future liver remnant. DRHF was defined based on a proposal by the International Study Group of Liver Surgery, as follows: an impaired ability of the liver to maintain its synthetic, excretory, and detoxifying functions, which are characterized by an increased PT INR and concomitant hyperbilirubinemia (considering the normal limits of the local laboratory) on or after postoperative day 5. The normal upper limits of PT and bilirubin in our institutional laboratory were 1.30 INR and 1.2 mg/dL, respectively. If either the PT INR or serum bilirubin concentration was preoperatively elevated, DRHF was defined by an increasing PT INR and increasing serum bilirubin concentration on or after postoperative day 5 (compared with the values of the previous day).

Statistical analysis plan

Between-group differences in preoperative and intraoperative characteristics and postoperative outcomes were compared using the Chi-square test or Fisher exact test for categorical variables and the Student *t* test or Mann-Whitney U test for continuous variables,

as appropriate. $P < 0.05$ was considered statistically significant. SPSS 23 (IBM Corp., Armonk, NY, USA) software was used for all statistical analyses.