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CLINICAL TRIAL REPORT

Dexmedetomidine Cannot Attenuate Liver Injury and Improve Outcomes Following Laparoscopic Living Donor Hepatectomy: A Randomised Controlled Trial

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Purpose: To determine the effects of intraoperative dexmedetomidine (DEX) administration on postoperative ischaemia/reperfusion injury (HIRI) and clinical outcomes of patients undergoing the laparoscopic living donor hepatectomy (LLDH).

Patients and Methods: Fifty-five patients who underwent the LLDH were randomly assigned to the DEX or control group. The DEX group received an intravenous infusion of DEX with an bolus dose of 1 μg/kg for 15 min before anaesthesia induction, followed by a continuous infusion at a rate of 0.4 μg/kg/h until the portal branch was disconnected. The control group was given an intravenous infusion of 0.9% saline at same volume and rate. The primary outcome was peak serum aspartate aminotransferase (AST) level during the first 72 h postoperatively. The secondary outcomes included other variables of postoperative liver and kidney function, intraoperative hemodynamic changes, postoperative recovery outcomes and the occurrence of complications.

Results: The peak serum AST level during the first 72 h postoperatively was not significantly different between groups (DEX vs control: 288 [194–466] vs 324 [194–437] IU/L; difference, −1.2 IU/L; 95% CI, −86.9 to 88.0; P=0.973). The intraoperative mean artery pressure was not significantly different, but intraoperative heart rate was significantly decreased in the DEX group. There were no significant differences between groups in other secondary outcomes.

Conclusion: This study demonstrates that intraoperative DEX administration at the studied dosage regimens cannot attenuate postoperative HIRI and does not improve clinical outcomes in patients undergoing the LLDH.

Clinical Trial Registration: www.chictr.org.cn, ChiCTR2000040629.

Keywords: laparoscopic living donor hepatectomy, hepatic ischemia/reperfusion injury, dexmedetomidine, postoperative recovery

Introduction

In 2002, Cherqui et al reported the first case of laparoscopic living donor hepatectomy (LLDH) for liver transplantation in a child with end-stage liver disease.[1] With the improvement of surgical techniques in recent years, laparoscopic donor left lateral sectionectomy has now been recognized as a standard practice and is supported by international consensus.[2,3] The adult LLDH has been undergoing for over 20 years in America, with over 4500 surgical cases in total.[4] By 2012, pure laparoscopic living left or right hemi-hepatectomy has also been reported in several studies worldwide.[5,6] The LLDH has both cosmetic and functional advantages for the donor,[7,8] but intraoperative bleeding is still a major risk associated with severe adverse outcomes.[9] The intermittent liver inflow occlusion, ie, Pringle's maneuver, is an effective maneuver commonly used for reducing blood loss during laparoscopic hepatectomy,[10] but it may inevitably lead to the development of hepatic ischaemia/reperfusion injury (HIRI).[11] For patients undergoing hepatectomy and liver transplantation, HIRI actually is an important pathophysiologic cause of liver injury and may significantly increase the risk of

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postoperative morbidity and mortality.[12–14] Furthermore, abnormal liver function after hepatectomy in healthy living liver donors is significantly associated with prolonged hospital stay, increased financial burden and postoperative morbidity.[15,16] Thus, preventing or attenuating the HIRI by hepatectomy to improve the safety and outcomes of donors deserves more attention.

As the mechanisms of HIRI are very complex and have not been fully elucidated,[17] effective treatment or preventive strategies of HIRI are still scarce. Dexmedetomidine (DEX) is a highly selective α2-adrenoreceptor agonist that has been extensively used in clinical practice.[18] Available literatures indicates that inflammation is an important pathophysiological mechanism of ischemia/reperfusion injury and nucleotide-binding domain-like receptor protein 3 (NLRP3) inflammasome plays a pivotal role in mediating inflammatory responses associated with ischemia/reperfusion injury and post-transplant rejection.[19,20] Experimental researches confirm that DEX can alleviate the HIRI by inhibiting the NLRP3 inflammasome and thus enhance liver regeneration and functional recovery after partial hepatectomy.[21–23] In recent years, some clinical studies also demonstrate that perioperative DEX administration may provide a protection against the HIRI after hepatectomy and living donor liver transplantation (LDLT).[24–28] Furthermore, the results of two retrospective studies from our center show that intraoperative DEX administration has the potential to decrease the risk of HIRI and is associated with a reduced incidence of moderate-to-severe HIRI in the pediatric patients undergoing the deceased liver transplantation.[29,30] However, there has been no study determining the effects of intraoperative DEX administration on postoperative liver injury and clinical outcomes of healthy adult patients undergoing the LLDH. Given above the beneficial effects of intraoperative DEX administration on postoperative liver function in patients with LDLT and hepatectomy, we hypothesized in this study that intraoperative DEX administration can provide a protection against the HIRI in the healthy adult patients with LLDH.

Methods

Ethics

This study protocol was approved by the Ethics Committee of Beijing Friendship Hospital at November 2, 2020 (Reference Number:2020-P2-208-02, Chairperson Prof. Miao-Rong Xie), and registered in the Chinese Clinical Trial Registry website (www.chictr.org.cn, ChiCTR2000040629) at December 4, 2020. Each surgery was also approved by the Ethics Committees of Beijing Friendship Hospital and Beijing Municipal Health Commission. The study was performed in accordance with the Consolidated Standards of Reporting Trials (CONSORT 2010) Guidelines[31] and the principles of the Declaration of Helsinki.

Participants

This prospective randomised controlled trial was conducted at the Beijing Friendship Hospital, Capital Medical University, Beijing, China, from December 10, 2020 to August 30, 2023. Each living liver donor voluntarily signed an informed consent to donate a portion of her or his liver in accordance with the Declaration of Istanbul. The patients aged 18–60 years with American Society of Anesthesiologists (ASA) grades I–II and undergoing the elective LLDH were screened for eligibility. The exclusion criteria included a history of severe allergy to DEX, conversion to open laparotomy, reduced liver size in vivo, and refusal of informed consent.

Randomisation and Masking

For all included living liver donors, they were told about the details of the study protocol and that they had the right to withdraw from the study at any time. After written informed consent was obtained from the included patients, they were randomly assigned to the DEX or control group at a 1:1 ratio using a computer-generated, random-sequence allocation list. The randomisation process was performed by an investigator who was not involved in the patient eligibility assessment or recruitment processes and data collection. The allocation sequence was concealed from the researchers at all sites by serially numbered, opaque, sealed envelopes. After patients entered into the operating room, a nurse anaesthetist who was not involved in the study opened the envelope containing the group allocation and prepared the study drugs in the identical 50-mL infusion syringes. Anaesthesiologists who did not participate in data collection

administered the study drugs. All other related medical staffs, investigators and patients were blinded to the group assignments.

Interventions

Patients in the DEX group received a loading dose of DEX (1 μg/kg) for 15 min followed by a continuous infusion (0.4 μg/kg/h). Intravenous infusion of DEX was started before anaesthesia induction and discontinued after the portal vein branch was disrupted. For patients in the control group, 0.9% saline was intravenously infused at same volume and rate with identical duration.

Anaesthesia and Surgical Management

All participants received the same anaesthetic management and surgical procedures according to the standard protocols of our institution. Other than standard monitoring including non-invasive blood pressure, heart rate (HR), pulse oxygen saturation (SpO_2), electrocardiogram and end-tidal carbon dioxide pressure ($P_{ET}CO_2$), an arterial catheter was also inserted into the right radial artery under local anaesthesia to monitor invasive blood pressure. Then, anaesthesia was induced with intravenous sufentanil (0.3–0.4 μg/kg), propofol (2 mg/kg) and cisatracurium (0.2 mg/kg). After successful intubation, anaesthesia was maintained with intravenous infusions of propofol (4–8 mg/kg/h), remifentanil (0.1–0.3 μg/kg/min), and cisatracurium (0.1 mg/kg/h). The depth of anaesthesia was monitored with the bispectral index (BIS), which was maintained between 40 and 60. The lungs of patients were mechanically ventilated using a volume-controlled model with a tidal volume of 6–8 mL/kg, 0.6 fraction of inspiration oxygen and respiratory rate of 12–18/min to maintain the $P_{ET}CO_2$ at 35 to 45 mmHg. Before surgery started, a double-lumen central venous catheter was inserted via the internal jugular vein under ultrasound guidance for monitoring of central venous pressure (CVP) and infusion of fluid.

During surgery, a low CVP strategy was implemented in all patients by reducing the CVP to less than 5 mmHg in the reverse-Trendelenburg position and limiting infusion of fluid at a rate of 1–1.5 mL/kg/h, with intravenous administration of furosemide (10–20 mg) and/or nitroglycerine (0.2–0.5 μg/kg/min). If mean artery pressure (MAP) was <60 mmHg, ephedrine (6–10 mg) and/or phenylephrine (25–50 μg) were intravenously administered and then noradrenalin was continuously infused at a rate of 0.02–0.1 μg/kg/min if needed. If HR was <50 beats/min, atropine 0.5 mg was intravenously injected. When liver tissue transection was completed, fluid infusion was no longer limited.

According to our routine practice,[32] the choice of graft type was determined on the basis of a comprehensive preoperative imaging assessment using the IQQA®-3D liver system. Key decision factors included a predicted graft-to-recipient weight ratio (GRWR) and remnant liver volume to standard liver volume (RLV/SLV). All donor hepatectomies were performed by the same surgical team under carbon dioxide pneumoperitoneum with a pressure of 10–13 mmHg. Furthermore, consistent surgical procedures for laparoscopic donor hepatectomy were carried out throughout the study period. During the liver resection, the intermittent Pringle's maneuver with one cycle of hepatic inflow occlusion for 10 min and reperfusion for 5 min was performed, and the number of occlusion cycles was determined by the surgeons, as needed. Hepatic parenchymal transection was performed by the same technique, and bile duct alignment was confirmed via the cholangiography before dissection. After the completion of hepatic parenchymal resection, a transverse incision was made 3 cm above the symphysis pubis, the vessels and biliary branches were clamped and dissociated sequentially, and the graft was preserved with histidine-tryptophan-ketoglutarate solution immediately after removal. At the end of surgery, all patients received wound infiltration with 20 mL of 0.5% ropivacaine for postoperative multimodal analgesia. After the closure of peritoneum, both tramadol hydrochloride (100 mg) and tropisetron (5 mg) were intravenously administered as postoperative analgesic and anti-emetic drugs. Extubation was carried out when patient was able to follow the instructions and spontaneous breathing was adequately resumed. Then patient was transferred to the post-anaesthesia care unit (PACU) for close observation until discharge criteria were reached.

After surgery, all patients received the standard postoperative care regimens. Flurbiprofen axetil 50 mg was intravenously administered twice a day. Additionally, patient-controlled analgesia was carried out with analgesic solution containing sufentanil 200 μg and ondansetron 32 mg in 0.9% sodium chloride of 200 mL, and analgesic pump was set up at a background infusion of 2 mL/h and a single bolus dose of 2 mL with a lockout time of 10 min. The Visual Analogue Scale scores of postoperative pain were kept to 4 or less.

Primary Outcome and Secondary Outcomes

The primary outcome was the peak serum aspartate aminotransferase (AST) level during the first 72 h postoperatively. The secondary outcomes were the serum alanine aminotransferase (ALT) and lactic dehydrogenase (LDH) levels within the first 72 h postoperatively, other variables related to liver and kidney function, anaesthesia-related data, surgical data, hemodynamic changes, postoperative recovery variables, length of hospital stay and postoperative complications.

Assessments

The biomarkers of liver injury, such as the serum AST, ALT, LDH and total bilirubin (TBIL) levels and coagulation parameters including the prothrombin time (PT) and activated partial thromboplastin time (APTT), were measured at five time points: day before surgery, at arrival in the PACU and daily for 3 days postoperatively. Kidney function variables including serum urea nitrogen (BUN) and creatinine (Cr) were also measured at the above mentioned time points. Demographic data and fatty liver disease status were noted preoperatively. Anaesthesia time, surgery time, graft weight, graft type, liver splitting time, ischemic time by the Pringle's maneuver, dosages of propofol and remifentanil, and intraoperative dosage of phenylephrine, fluid volume, urine output, blood loss and blood transfusion volume were measured. Hemodynamic changes including MAP and HR, and BIS were recorded before surgery, before intubation, 5 min after intubation, 30 min and 1 hour after the initiation of surgery, at the end of the first Pringle's maneuver, 5 min after resection, at the end of surgery and at discharge of the PACU. Postoperative complications during the first 30 days after surgery were recorded and categorized based on the Clavien-Dindo classification.[33] Minor complications were defined as grade I to II, whereas major ones were defined as grade III to V complications. The delayed recovery of hepatic function was defined as follows: the presence of a PT > 20 s or serum TBIL > 50 μmol/L on postoperative days 1–5 (excluding obstructive jaundice).[34]

Statistical Analysis

The sample size was calculated based on the primary outcome, that is, the peak serum AST level during the first 72 h postoperatively. According to the results of a previous study in patients undergoing hepatectomy,[24] the postoperative peak serum AST level was 195.8 (110.4) IU/L in the DEX group and 255.1 (140.8) IU/L in the control group, respectively. A difference of 40 IU/L in the postoperative peak serum AST is considered to be clinically significant. Using the PASS 15.0 software, assuming a power of 80% with an alpha of 0.025 to detect a difference of 40 IU/L in the postoperative peak serum AST level, 26 patients in each group were required. Considering a potential dropout rate of 5%, a final sample size of 56, ie, 28 patients in each group, was determined.

Quantitative data are presented as the mean (standard deviation, SD) or median (interquartile range, IQR) and their between-group comparisons were performed using Student's *t* test or the *Mann–Whitney U*-test according to the normality of the data. Qualitative data are presented as frequencies or percentages and their between-group comparisons were done using the *Chi-square* test or *Fisher's* exact test. The *Mann–Whitney U*-test was used to compare the between-group difference in the primary outcome. Generalized estimating equations were used to compare the between-group differences in the TBIL, AST, ALT, LDH, renal function, coagulation parameters and hemodynamic variables. The pseudomedian difference was calculated using the Hodges–Lehmann estimate, which is based on the *Mann–Whitney U-test*. The odds ratios (or difference) and 95% CI were also calculated. For all analyses, a two-sided $P < 0.05$ was considered to indicate statistical significance. All the statistical analyses were performed by The SPSS software 23.0 and PRISM 10.0 and completed by the specialized statisticians who were from the Clinical Research Institute of Beijing Friendship Hospital and blinded to grouping assignment of patients.

Results

Patients' Characteristics, Anaesthesia and Surgery Data

The flowchart of included and excluded patients according to the Consolidated Standards of Reporting Trials statement is displayed in Figure 1. A total of 74 donors were screened for eligibility, 16 of them did not meet the inclusion criteria. The remaining 58 donors were randomly allocated to the DEX group (n = 29) or control group (n = 29). In the DEX group, two donors were further excluded after randomisation because one had the biliary tract injury during surgery, and

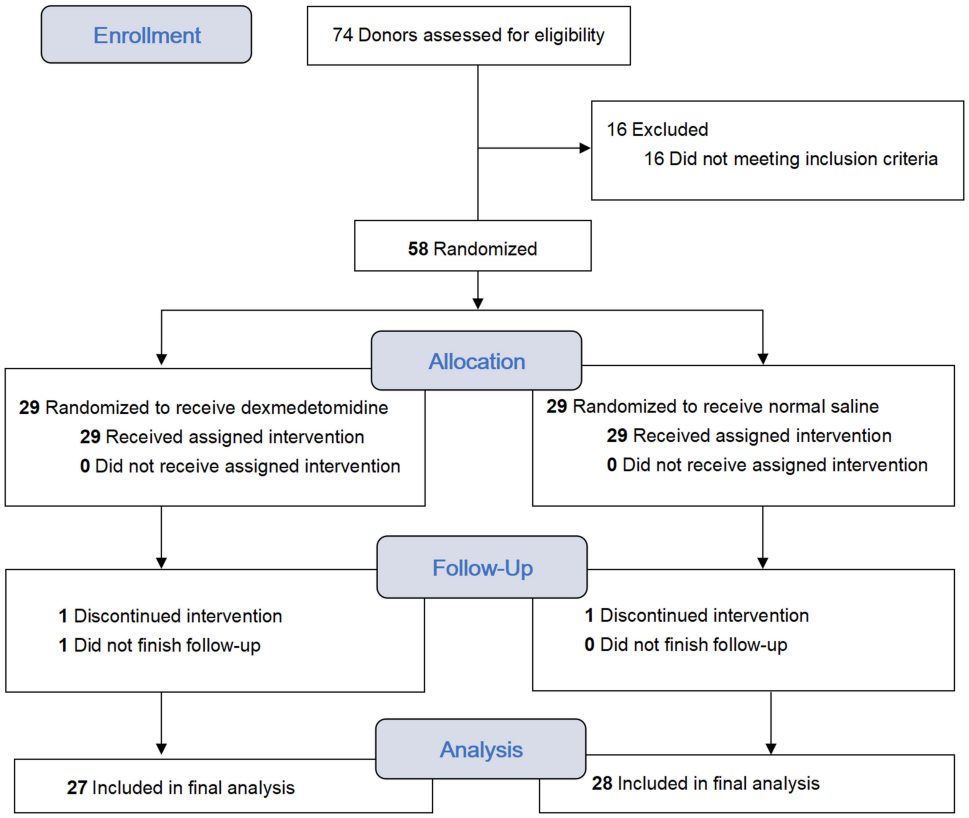

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flowchart.

another was lost of postoperative follow-up. In the control group, one donor was also excluded after randomisation because of intraoperative major bleeding from a ruptured vena cava. Finally, 55 donors (27 in the DEX group and 28 in the control group) were included in the final data analysis.

Two groups were comparable with respect to the demographic and baseline characteristics of patients (Table 1). Anaesthesia time, surgery time, graft types, graft weights, ischemic time, liver split times, blood loss and transfusion volumes, and extubation time were not significantly different between groups, but intraoperative dosages of propofol and

Table 1 Demographic and Baseline Characteristics of Patients

Variables	DEX Group (n=27)	Control Group (n=28)	P values
Age (years), mean (SD)	33.7(6.0)	32.8(6.7)	0.450
Female sex, n (%)	8(28.6)	14(50)	0.101
Height (cm), median (IQR)	170(163–175)	170(163–177)	0.989
Weight (kg), mean (SD)	67.2(11.1)	67.9(11.6)	0.971
BMI (kg/m^2), mean (SD)	23.3(2.6)	23.5(2.9)	0.609
ASA physical status, n (%)			1.000
I	25(92.6)	26(92.9)	
II	2(7.4)	2(7.1)	
Comorbidities, n (%)			
Hypertension	1(3.7)	1(3.6)	1.000
Diabetes mellitus	1(3.7)	0	0.491
Fatty change in the liver	9(32.1)	9(32.1)	1.000

Notes: Values are presented as mean (SD), median (IQR), or number of patients (%).
Abbreviations: DEX, dexmedetomidine; BMI, body mass index; SD, standard deviation; IQR, interquartile range.

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Table 2 Anaesthesia and Surgery Data

Variables	DEX Group (n=27)	Control Group (n=28)	P values
Anaesthesia time (min), mean (SD)	285(67)	297(59)	0.497
Surgery time (min), mean (SD)	234(67)	245(61)	0.546
Type of graft, n (%)			0.295
Left lateral lobe	24(88.9)	21(75.0)	
Left lobe	3(11.1)	7(25.0)	
Graft weight (g), mean (SD)	266.6(60.6)	277.3(66.4)	0.534
Liver split time (min), mean (SD)	42.6(18.6)	54.0(27.2)	0.076
Ischemic time (min), median (IQR)	24.5(20.3–32.8)	25.0(17.0–35.0)	0.889
Remifentanil (mg), median (IQR)	2.5(2.0–2.9)	3.3(2.5–3.6)	0.017
Propofol (mg), mean (SD)	1128 (386)	1401(440)	0.019
Urine output (mL), median (IQR)	650(450–850)	300(200–415)	<0.001
Blood loss (mL), median (IQR)	80(50–120)	50(50–100)	0.145
Blood transfusion (mL), median (IQR)	2000(1700–2200)	1800(1700–2000)	0.275
Phenylephrine (μg/kg), median (IQR)	5.6(2.6–9.7)	1.5(0.7–6.1)	0.034
Extubation time (min), median (IQR)	20(16–32)	20(12–27)	0.673

Notes: Values are presented as mean (SD), median (IQR), or number of patients (%).
Abbreviation: DEX, dexmedetomidine.

remifentanil were significantly decreased and dosage of phenylephrine and urine output were significantly increased in the DEX group compared with the control group (Table 2).

Primary and Important Secondary Outcomes

There was no significant difference in the peak serum AST level during the first 72 h postoperatively between groups. The peak serum ALT and LDH levels during the first 72 h postoperatively, and proportion of patients with delayed recovery of liver function were also not significantly different between groups (Table 3).

Secondary Outcomes

The liver and renal function variables at different time points are shown in Figure 2 and Supplement Table 1. The serum AST, ALT, LDH, TBIL, Cr and BUN levels, PT and APTT during the first three postoperative days were not significantly different between groups.

The changes of hemodynamic parameters at different time points are shown in Figure 3. Compared to the control group, the DEX group had a significantly higher MAP during tracheal intubation and a significantly lower MAP during the PACU stay ($P = 0.004$). Heart rate was significantly lower in the DEX group than in the control group throughout the surgical procedure and during the PACU stay ($P = 0.000$). The BIS values before and after intubation were significantly decreased in the DEX group.

The length of hospital stays, time to first flatus and the occurrence of postoperative complications were not significantly different between groups (Supplement Table 2).

Table 3 Primary and Important Secondary Outcomes

Variables	DEX Group (n=27)	Control Group (n=28)	OR or Difference (95% CI)	P values
Primary outcome				
Peak AST (IU/L), median (IQR)	288(194–466)	324(194–437)	−1.2(−86.9 to 88.0)	0.973
Important secondary outcomes				
Peak ALT (IU/L), median (IQR)	438(217–786)	369(253–704)	22.5(−135 to 195)	0.827
Peak LDH (IU/L), median (IQR)	392(323–546)	362(323–473)	25(−36 to 88)	0.426
Delayed recovery of liver function, n (%)	4(14.8)	5(17.9)	0.80(0.190 to 3.36)	1.000

Notes: Values are presented as median (IQR), or number of patients (%).
Abbreviations: DEX, dexmedetomidine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactic dehydrogenase.

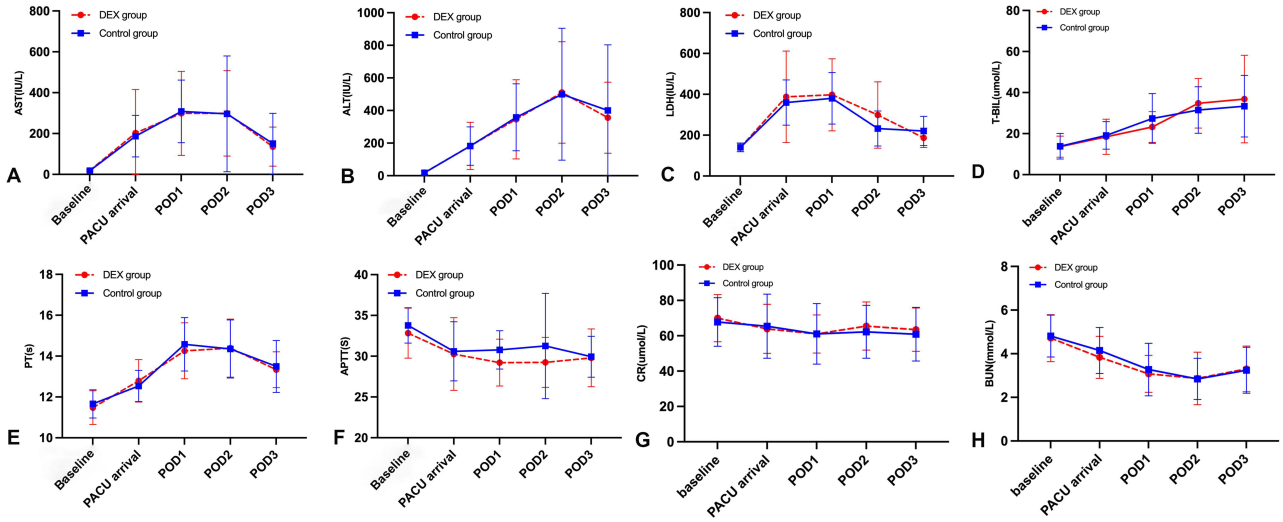

Figure 2 Secondary outcomes including liver and renal function variables at different time-points. (**A**) AST; (**B**) ALT; (**C**) LDH; (**D**) TBIL; (**E**) PT; (**F**) APTT; (**G**) Cr; (**H**) BUN.

Abbreviations: DEX, dexmedetomidine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactic dehydrogenase; TBIL, total bilirubin; PT, prothrombin time; APTT, activated partial thromboplastin time; Cr, serum creatinine; BUN, blood urea nitrogen; PACU, post-anesthesia care unit; POD, postoperative day.

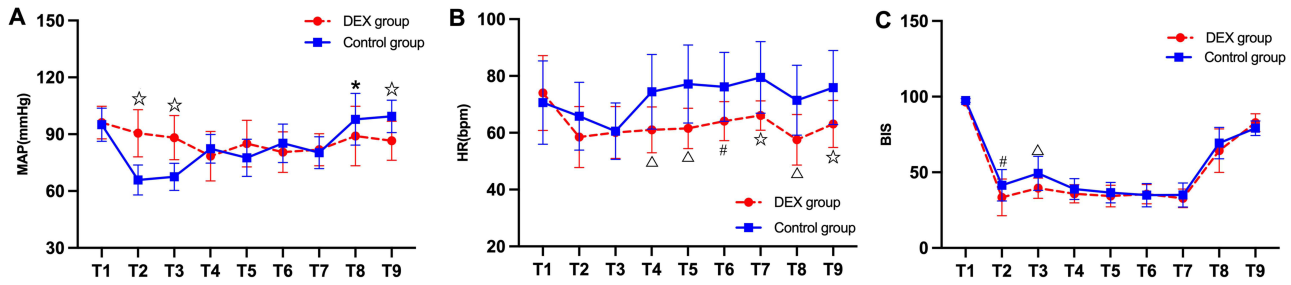

Figure 3 Hemodynamic changes and anaesthetic levels at different time points. (**A**) MAP; (**B**) HR; (**C**) BIS. T1, baseline; T2, before intubation; T3, 5 min after intubation; T4, 30 min after initiation of surgery; T5, 1 hour after initiation of surgery; T6, completion of first Pringle's maneuver; T7, 5 min after resection; T8, the end of surgery; T9, discharge of PACU. Data were expressed as mean ± SD. *$P<0.05$; #$P<0.01$; ☆$P<0.001$; △$P<0.0001$.

Abbreviations: MAP, mean artery pressure; HR, heart rate; BIS, bispectral index; PACU, post-anaesthesia care unit; DEX, dexmedetomidine.

Discussions

This study aimed to determine the effects of intraoperative DEX administration on postoperative HIRI and clinical outcomes in the healthy patients who underwent the LLDH. The results showed that intraoperative DEX administration did not provide any favorable effect on early postoperative liver function variables. Furthermore, extubation time, the incidence of delayed recovery of liver function, postoperative hospital stay and time to first flatus were not significantly different between groups. These results indicate that intraoperative DEX administration does not product a significant protection against the HIRI during the LLDH and cannot improve the postoperative outcomes. Thus, this study does not validate our hypothesis.

Available experimental evidence indicates that HIRI is characterized by significant oxidant stress and inflammatory response[35,36] and DEX can attenuate ischaemia/reperfusion injury and provide a protection against organ injury by anti-inflammatory and antioxidant effects.[37] Most important, several clinical trials also provide evidence that perioperative DEX administration product a protection against the HIRI after hepatectomy. A propensity score-matched retrospective study including 494 patients with liver disease who underwent partial hepatectomy showed that intraoperative DEX administration significantly decreased the serum ALT and LDH levels in the early postoperative period, indicating that DEX exerts a protective effect on postoperative liver function.[38] In a prospective, randomised double-blind clinical trial including 44 patients who underwent elective hepatectomy with hepatic inflow occlusion maneuver, Wang et al[25]

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demonstrated that perioperative DEX administration with a loading dose of 1 μg/kg over 10 min followed by a maintenance dose of 0.3 μg/kg/h was able to significantly mitigate intestinal and hepatic injuries. In another prospective, randomised, single-blind controlled study including 58 patients who underwent hepatectomy, Zhang et al[24] similarly showed that regardless of with or without hepatic inflow occlusion maneuver during surgery, intraoperative DEX administration with a loading dose of 0.5 μg/kg for 10 min and a continuous infusion at a rate of 0.5 μg/kg/h until resection of liver lobes significantly decreased the serum level of α-glutathione S-transferase at 0.5 h after resection of liver lobe, and the serum levels of ALT and AST at 2 h and 24 h postoperatively, suggesting that DEX provides a protection against postoperative liver injury. In a prospective controlled, double-blinded, randomised study including 50 patients who underwent partial hepatectomy with inflow occlusion, Taman et al[26] showed that continuous infusion of DEX at a rate of 0.3 μg/kg/h without a loading dose from the completion of tracheal intubation to the end of surgery exerted a protective effect on postoperative liver function, shown by decreased serum TBIL, AST and ALT levels and increased serum albumin level. Especially, a meta-analysis of 8 randomised controlled trials including 468 patients also confirm that perioperative DEX administration can produce a protective effect on the HIRI after hepatectomy, with decreased serum levels of ALT, AST, TBIL and malondialdehyde and increased serum superoxide dismutase activity.[27]

However, the results of our clinical study in patients undergoing the LLDH are not in agreement with the findings of above clinical trials. In this study, the serum enzymatic biomarkers including AST, ALT and LDH were applied as primary and important secondary outcomes to determine postoperative liver injury. The results showed that the peak serum levels of these liver injury biomarkers within first 72 h postoperatively were not significantly different between groups. Furthermore, there were no significant between-group differences in other liver function variables obtained at different postoperative time points, as well as proportion of patients with delayed recovery of liver function.

The detailed reasons of different results among previous and our studies are unclear, but they may be attributable to several factors. First, different study populations may be an important contributing factor. The participants of previous studies are the patients undergoing partial hepatectomy because of hepatic tumors or parenchymatous diseases. Except for older ages, these patients often suffer from hepatic cirrhosis, steatosis or structure disorders with significant sinusoidal hemodynamic changes, microcirculation impairment and metabolic dysfunction. Thus, they maybe more vulnerable to the liver injury by surgical procedures.[39,40] In contrast, the living liver donors are often healthy young individuals who are identified by rigorous preoperative assessments. For example, only one-third of the donors in this study have a mild hepatic steatosis. Consequently, these patients may have a stronger tolerance to the liver injury by surgical procedures, and the extent of liver injury induced by intraoperative ischaemia might not be severe enough to cause significantly increases of serum liver injury biomarkers. Furthermore, mild liver injury may obscure the opportunity to identify the protective effect that DEX provides by inhibiting inflammatory and oxidative stress responses. This could be a major reason of no significant differences in postoperative serum levels of liver injury biomarkers between groups in this study. In a randomised, controlled trial study of 62 patients undergoing the elective LDLT, Shin et al[41] used the peak serum levels of liver transaminases including ALT and AST during the first 7 days after surgery as primary outcomes and failed to find any protective benefit of propofol on the postoperative HIRI. They consider that a possible reason for this negative result also is that the HIRI induced by the LDLT is not enough to produce significant changes of serum liver injury biomarkers. Thus, for healthy patients with a low risk of severe liver injury during surgery, the protective effect of intraoperative DEX may be clinical insignificant. In fact, our study also demonstrated that intraoperative DEX administration did not improve postoperative recovery parameters including the time to first flatus and length of hospital stay, and did not decrease the severity of postoperative complications. These results are consistent with the findings of previous studies, in which intraoperative DEX administration can significantly decrease the postoperative serum levels of liver injury biomarkers, but does not improve postoperative outcomes of patients undergoing partial hepatectomy.[24–27,38]

Second, available evidence indicates that DEX provides dose-dependent organ protection.[42–44] Thus, the dose and timing of DEX administration may have influenced the outcomes of various studies. It is generally believed that pharmacological preconditioning remains a promising therapeutic strategy for attenuating HIRI.[45] Furthermore, the early phase of reperfusion injury is defined as the first 2 h after reperfusion, and involves the activation of inflammatory cells, excessive release of proinflammatory cytokines and significant production of reactive oxygen species, which are responsible for more severe tissue damage in the late phase of reperfusion injury.[46] Given that the half-life of DEX is

approximately 2 h,[47] the protocol of this study was to start DEX administration before induction of anaesthesia or the onset of intraoperative HIRI and then maintain intravenous infusion until the completion of portal branch dissection. In the previous works,[25–27,38] however, DEX administration was often continued to the end of surgery. It has been shown that a prolonged use of DEX or a 24 h perioperative infusion of DEX may reduce the incidence of delayed graft function after kidney donation after cardiac death.[48] Thus, more researches are needed to determine whether a continuous infusion of DEX throughout the surgical procedure or perioperative period would produce more favorable outcomes on postoperative liver function of patients undergoing the LLDH.

Third, previous works used more observed time points in the first postoperative day, such as 2 h, 6 h, 12 h and 24 h postoperatively, and showed that intraoperative DEX administration significantly reduced serum levels of liver injury biomarkers within 24 h postoperatively.[24–26,38] However, our study measured serum levels of liver injury biomarkers at arrival in the PACU and daily for 3 days postoperatively. It is unclear if this design of less observed time points in the first postoperative day could miss the opportunity to reveal the protective effects of intraoperative DEX administration on early postoperative liver function of patients undergoing the LLDH.

It is worth noting that postoperative serum Cr and BUN levels were not significantly different between groups, but intraoperative urine output was significantly increased in the DEX group compared with the control group. This may be attributable to the ability of DEX to act as a diuretic and improve renal function.[49] As previously reported,[50] moreover, this study showed that intraoperative DEX administration significantly reduced the dosages of propofol and remifentanil without affecting the time to emergence or extubation.

It is reported that common adverse effects of DEX are hypotension and bradycardia.[51] In this study, MAP during anaesthesia induction and intubation was significantly decreased in the DEX group. This may be due to the use of a loading dose DEX. The MAP during surgery was not significantly different between groups, albeit intraoperative dosage of phenylephrine was significantly increased in the DEX group. Furthermore, HR was significantly decreased throughout surgery in the DEX group, but no severe bradycardia was observed in the two groups. These results indicates that the use of DEX as a general anaesthetic adjuvant for the LLDH may be helpful to enhance surgical stress inhibition and stabilize intraoperative hemodynamic variables.

This clinical study has several limitations that deserve special attention. First, this was a single-center randomised controlled trial with a small sample size. It may be not power to show significant between-group differences of clinical outcomes, as the sample size was evaluated based on the primary outcome, that is, postoperative serum AST level. As surgical procedures, liver resection weight and surgical complications can significantly affect the occurrence and severity of postoperative liver injury, the findings of this study should not be extrapolated into the other surgical patients who are different from the participants of our study. Second, other than liver injury, the serum AST level may also increase when injuries of myocardium, skeletal muscles and kidneys occur. Thus, the primary outcome of the study, the peak serum AST level during the first 72 h postoperatively, is a surrogate endpoint of liver injury, rather than a gold standard variable of liver injury. This may decrease the ability to validate beneficial effects of intraoperative DEX administration on postoperative liver function. Third, both oxidative stress and excessive inflammatory responses have been regarded as the two pivotal mechanisms of HIRI after hepatectomy and liver transplantation.[35] Furthermore, perioperative DEX administration has been shown to attenuate oxidative stress and systemic inflammatory responses associated with HIRI in patients undergoing elective hepatectomy with inflow occlusion.[25,52] Given that this study mainly focused on postoperative liver function and clinical outcomes of patients, we did not further evaluate the possible influences of DEX on postoperative oxidant stress and inflammatory biomarkers. Fourth, a single-dose scheme of intraoperative DEX administration was designed. The important questions that this study cannot answer are whether protective effect of DEX on the HIRI are the dose-dependent and the duration of DEX administration can significantly affect protective effect of DEX on the HIRI. Fifth, the mechanisms of HIRI by surgical procedures are complex and alone intraoperative DEX administration may not adequately protect against HIRI in the healthy patients undergoing the LLDH. Recently, a randomised controlled trial conducted in patients with cirrhosis undergoing laparoscopic hepatectomy for liver cancer demonstrates that ulinastatin combined with DEX compared with alone administration of two drugs can provide an enhanced protection against HIRI possibly through a synergistic effect against oxidative stress and inflammatory response.[52] Evidently, this study cannot provide any clues regarding the potential benefits of DEX combined with

other interventions on postoperative HIRI of living liver donors. Thus, further studies with well design and large sample sizes are still needed to address above issues.

Conclusions

In conclusion, this randomised controlled trial does not demonstrate the evidence that intraoperative DEX administration can attenuate postoperative HIRI and improve clinical outcomes in healthy patients undergoing the LLDH. This finding does not support the routine use of intraoperative DEX for preventing HIRI in the patients undergoing LLDH, but future multicenter studies with larger sample size and longer follow-up period are needed to determine the potential benefits and risks of different-dose DEX or DEX combined with other protective strategies in the patients who undergo the LLDH and are at a high risk for HIRI.

Data Sharing Statement

Individual deidentified participant-level data underlying the results reported in this article, as well as the study protocol and statistical analysis plan, will be made available upon reasonable request. Data are available beginning 3 months after online publication and for up to 24 months thereafter. To request data, please contact the corresponding author (Prof. Fu-Shan Xue). Requests must include a methodologically sound proposal, and approval will be at the discretion of the study investigators.

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Disclosure

The authors report no conflicts of interest in this work.

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