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Comparison of Cardioprotective Effects of Propofol versus Sevoflurane in Pediatric Living Donor Liver Transplantation

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

A Yiqi Weng*
BCE Shaoting Yuan*
D Hongxia Li
FG Wenli Yu

Department of Anesthesiology, Tianjin First Center Hospital, Tianjin, P.R. China

* Yiqi Weng and Shaoting Yuan are the co-first authors

Corresponding Author: Wenli Yu, e-mail: cbs_baosen@126.com
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Background: Our study compared the myocardiac protective effect of propofol *vs.* sevoflurane in pediatric patients receiving living donor liver transplantation (LDLT) surgery.

Material/Methods: We randomly and equally divided 120 children who underwent LDLT into a sevoflurane group and a propofol group. Preoperative, intraoperative, and postoperative data were collected and compared between the 2 groups. The concentrations of cTnI, CK-MB, IL-6, TNF-α, and HMGB1 at 5 min after induction (T0), 30 min in the anhepatic period (T1), and 3 h after reperfusion (T2), and at the end of surgery (T3) were measured.

Results: There was no statistically significant difference in the characteristics of children in the 2 groups. Compared with T0, the levels of IL-6 and TNF-α at T1, T2, and T3 were higher, while the HMGB1 at T2 and T3 were higher ($P<0.05$). A similar trend for IL-6, TNF-α, and HMGB1 at different time points in the 2 groups was observed. Compared with T0, the cTnI and CK-MB at T2 and T3 were significantly higher ($P<0.05$), but there was no significant difference at different time points in the 2 groups. For the adverse events, there was no significant difference between the 2 groups.

Conclusions: Our study shows that the cardioprotective effect in pediatric patients undergoing living donor liver transplantation is similar with propofol and sevoflurane anesthesia.

MeSH Keywords: **Anesthetics, Inhalation • Hospitals, Pediatric • Liver Transplantation • Myocardial Ischemia • Propofol**

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Background

Liver transplantation is the only effective treatment for end-stage liver disease, and it has become the routine clinical treatment. The incidence of perioperative myocardial injury in liver transplantation patients is 40.4% and the mortality of patients with myocardial injury is as high as 11.4% [1], which seriously affect the prognosis and quality of life of patients. Compared with adults, liver function reserve is poor in children and the ventricular compliance is also low. Of particular importance, the contractility related myocardium is poorly developed and the cardiac functional restore is diminished due to being more vulnerable to cardiac injury. Previous studies suggested that sevoflurane and propofol possess different degrees of myocardial protection in pediatric cardiac surgery [2–4]. In the present study, the myocardioprotective effect of propofol *vs.* sevoflurane was compared in pediatric patients undergoing living donor liver transplantation (LDLT). Extensive studies have demonstrated that plasma cardiac troponin-I (cTnI) and creatine kinase isozyme (CK-MB) are sensitive indicators of myocardial injury [5,6], which were used as the main markers of myocardial injury in our study. We also assessed levels of representative inflammatory markers – interleukin (IL)-6, TNF-α, and HMGB1 – at various time points.

Material and Methods

Experimental condition

Our research was examined and approved by our Institutional Ethics Committee (Tianjin First Center Hospital, Tianjin, China, approval number 2018N075KY.). Informed consent was obtained from 120 parents whose children were scheduled for living donor liver transplantation from July 2018 to April 2019. The pediatric patients enrolled in the study were ASA (American Society of Anesthesiologists) III–IV, age 5–24 months, with no history of congenital heart disease or abnormal heart, lung, and kidney function. The children were randomly and equally divided into the sevoflurane group (S group) or the propofol group (P group) using a random number table.

Perioperative management

Anesthetic technique

Patients did not eat or drink before surgery. A peripheral venous passage was established and ECG, SPO2, NIBP, and heart rate were monitored after entry into the operating room. All patients were induced with midazolam 0.2 mg/kg and fentanyl 3 μg/kg. Cisatracurium besylate 0.2 mg/kg was given to assist subsequent tracheal intubation. Mechanical ventilation was implemented smoothly by 50–60% oxygen with a tidal volume of 8–10 ml/kg. Exhaled carbon dioxide pressure (30–40 mmHg) was controlled by modulating the respiratory rate at 20–28 breaths/min. The right internal jugular vein cannulation was accomplished using a Doppler ultrasound instrument (Philips Ultrasonic System CX50 POC, Royal Dutch Philips Electronics, Netherlands), manipulated by an experienced anesthesiologist. The invasive radial arterial pressure and central venous pressure were monitored throughout the operation.

Notably, in the sevoflurane group and propofol group, maintenance of anesthesia was carried out separately by inhaled sevoflurane (2.6–4.0%) and intravenous propofol (9–15 mg/(kg/h)). All patients could receive fentanyl (1–3 μg/kg) intravenous injection as needed and cisatracurium besylate continuous pumping at 1–2 μg/(kg/min) guided by bispectral index (BIS) monitoring. The BIS was controlled at 40–50. All patients were protected from hypothermia using a fluid warmer (Astotherm Plus 260; Stihler Electronic, Stuttgart, Germany) and a forced-air warming blanket (Bair Hugger, model 55501/52200; 3M, St. Paul, MN, USA).

Data recorded

All patients were immediately transferred to the ICU with endotracheal intubation after surgery, and were extubated as soon as they could maintain adequate spontaneous respiration and had adequate muscle strength on room air. Subsequently, time of mechanical ventilation and the length of ICU/hospital stay were recorded. Data on the entire operation, such as portal vein blocking time, inferior vena cava blocking time, and surgery time, were promptly recorded. In addition, doses of vasoactive agents during the operation and after admission to the ICU were documented. We recorded the following adverse events during the perioperative period: (1) hypertension (blood pressure increased by 30% or more from the baseline value for more than 5 min), treated by using nitroglycerin solution infusion 5 μg/min; (2) hypotension (blood pressure decreased by 30% or more from the baseline value for more than 5 min), treated by using epinephrine intravenous injection 1–2 μg or continuous intravenous pumping of dopamine at 2–5 μg/(kg/min), (3) myocardial ischemia (MI) (ST segment depressed or elevated greater than 1 mm and lasting longer than 5 min), treated by finding the etiology and taking appropriate measures to bring it back to normal; and (4) ventricular premature beat (VPB), treated by finding the etiology and taking appropriate measures to bring it back to normal.

Experimental parameters

Blood samples were collected from the right internal jugular vein of all patients at 4 different time points: 5 min after induction (T0), 30 min into the anhepatic period (T1) and 3 h after reperfusion (T2), and at the end of operation (T3). Blood samples

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Table 1. Patient characteristics.

Characteristics	Propofol (n=60)	Sevoflurane (n=60)	P
Age (m)	8.9±2.9	9.3±3.8	0.764
Weight (kg)	8.1±2.2	7.6±1.6	0.804
Height (cm)	64.5±7.1	67.4±7.9	0.907
Gender (male,%)	49.7%	43.6%	0.494
Postreperfusion syndrome (%)	11.2%	15.9%	0.267
Baseline hematocrit (%)	28.5±3.2	29.3±3.9	0.878
Baseline INR	1.4±0.6	1.5±0.7	0.479
Portal vein blocking time (min)	51.6±9.7	55.6±17.5	0.128
Inferior vena cava blocking time (min)	27.9±14.8	24.8±12.4	0.202
Surgery time (hr)	7.9±1.1	8.2±1.3	0.708
Red blood cell transfusion (in unit)	2.2±1.1	2.1±1.0	0.945
Fresh frozen plasma (mL)	354.8±167.0	355.8±146.9	0.849
Blood loss volume (mL)	356.7±169.9	386.7±149.7	0.225
Urine volume (mL)	495.7±283.4	442.2±244.5	0.179
BNP at postoperative time	1251.0±938.3	1482.5±1267.6	0.311
Length of postoperative hospitalization (d)	23.6±12.2	25.5±7.5	0.346
Icu stay time (d)	3.7±2.1	3.8±2.1	0.933
Duration of mechanical ventilation time (hr)	2.5±1.1	2.7±1.4	0.764
30d mortality	0	0	

Data are given as mean±SD.

were prepared according to the instructions to measure the biomarkers of myocardial injury (cTnI and CK-MB) and the inflammatory factors (IL-6, TNF-α, and HMGB1). The levels of cTnI and CK-MB were determined using an Access2 electrochemical luminescence apparatus following the manufacturer's instructions (Beckman-Coulter, USA). The concentrations of IL-6, TNF-α, and HMGB1 were assessed by enzyme-linked immunosorbent assay (ELISA) (reagent kit provided by Shanghai Biovol Biotechnology Co., China).

Statistical analysis

Analysis was performed using the statistical package SPSS19.0 (SPSS Inc, Chicago, IL, USA). We used the *t* test for unpaired values to assess differences in patient characteristics. The serial comparisons in serum parameters between the 2 groups were analyzed using repeated-measures two-way ANOVA with a post hoc test, considering multiple comparisons in each group and between the 2 groups. All data are expressed as mean±SD, and differences between means were considered significant if p was equal to or less than 0.05.

Results

Our study included a total of 120 pediatric patients undergoing living donor liver transplantation. There were no statistically significant differences in the patient characteristics of children between the 2 groups (Table 1).

Compared with T0, the levels of IL-6 and TNF-α at T1, T2, and T3 were higher, and HMGB1 at T2 and T3 were higher (P<0.05). A similar trend for IL-6, TNF-α, and HMGB1 at different time points in the 2 groups was also observed (Figure 1).

Compared with T0, cTnI and CK-MB at T2 and T3 were significantly higher (P<0.05), but there were no significant differences at different time points in the 2 groups (Figure 2). There were also no significant differences in adverse events between the 2 groups (Table 2).

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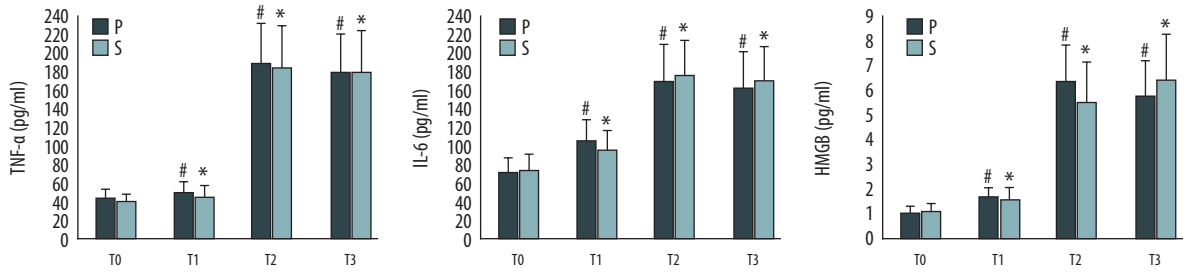

Figure 1. The markers of inflammation of the 2 groups. Bars represent mean±SD. # *P*<0.05 compared with T0 in P group; * *P*<0.05 compared with T0 in S group (n=60/group).

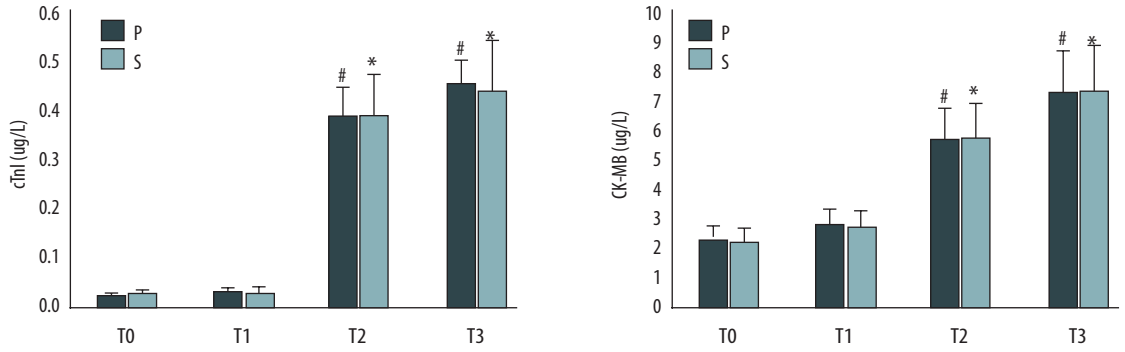

Figure 2. The markers of myocardial injury of the 2 groups. Bars represent mean±SD. # *P*<0.05 compared with T0 in P group; * *P*<0.05 compared with T0 in S group (n=60/group).

Table 2. Incidence of cardiovascular adverse events (n=60, %).

Group	Hypertension	Hypotension	MI	VPB
Propofol	6	36	14	7
Sevoflurane	2	45	12	8

Discussion

Our study shows that the myocardial-protective effect of propofol and sevoflurane anesthesia in pediatric patients undergoing living donor liver transplantation is similar. Living donor liver transplantation in children is relatively complicated, and the recipient's inferior vena cava needs to be blocked after entering the anhepatic period, which can easily lead to decreased blood volume, oxygen supply, and cardiac output. A myriad of studies showed overwhelming evidence that both cTnI and CK-MB are sensitive and specific indicators of myocardial cell injury [7–9]. We have demonstrated in our study that cTnI and CK-MB increased dramatically during the reperfusion period, indicating that myocardial injury occurred in the early neohepatic stage in pediatric living donor liver transplantation.

Proinflammatory cytokines can modulating cardiovascular function by various mechanisms. It is now known that virtually every nucleated cell type in the myocardium, including cardiac myocytes, can secrete proinflammatory cytokines in response to various myocardial damage or stressors [10]. It has been demonstrated that IL-6 shows cardio-depressive properties [11]. In patients with systolic heart failure, IL-6 and TNF-α are associated with functional NYHA class [12]. Furthermore, IL-6 and TNF-α have been shown to be independent predictors of mortality in heart failure [13]. Previous studies showed the critical role of HMGB1 in JAK/STAT and JNK signaling [14,15] and its potential to induce cardiomyocyte apoptosis by triggering the JNK pathway. Moreover, recent studies have shown that activation of the HMGB1-RAGE axis is important in mediating leukocyte accumulation and in determining the subsequent tissue damage [16,17]. In particular, this axis has a major role in early ischemia/reperfusion (I/R) damage, in which

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prolonged activation of the proinflammatory pathways increases myocardial injury [18,19]. Consistent with the above evidence, our study shows that the plasma levels of inflammatory cytokines IL-6, TNF-α, and HMGB1 in both groups were higher throughout the hepatic perfusion period, and these levels tended to coincide with the levels of cTnI and CK-MB, indicating that myocardial injury may be related to excessive release of inflammatory factors. Based on the above, this topic warrants further study.

Propofol decreases post-ischemic myocardial mechanical dysfunction, infarct size, and histological degeneration. It also suppresses the activity of neutrophils, and may therefore produce its beneficial effects by reducing free radicals, Ca^{2+} influx, and neutrophil activity [20]. Volatile anesthetics improve recovery of contractile function of the stunned myocardium. Sevoflurane preconditioning exerts cardioprotection and inhibits p38 activation in an AMPK-dependent manner with increased ERK1/2 activation, which may be an effective approach to reducing perioperative cardiac injury in diabetic patients [21]. Studies of sevoflurane in adults and in healthy children suggest that it may have significant advantages in infants and children with heart disease [22,23]. Nonetheless, to the best of our knowledge, the protective effects and mechanisms of propofol *vs.* sevoflurane on the hearts of children undergoing LDLT has previously been unclear. The present study compared the levels of IL-6, TNF-α, HMGB1, cTnI, and CK-MB between a propofol group and a sevoflurane group and found no significant differences, suggesting they have similar myocardium-protective effects in pediatric living donor liver transplantation.

There are several limitations in our study. Firstly, although the patients were randomly assigned to the propofol group or the sevoflurane group, the anesthesiologists could not operate entirely blinded to the anesthetic technique. Nevertheless, the researchers who collected the experimental data were blinded to the randomization. Secondly, the patient follow-up only assessed 30-day mortality. Therefore, a longer follow-up and more programs are needed for further study. Another limitation was that this was a single-center trial, and a multi-center clinical study is needed to verify our conclusions.

Conclusions

Our study shows that propofol and sevoflurane anesthesia have similar myocardial-protective effects in pediatric patients undergoing living donor liver transplantation.

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