Research Paper

The Application of Remimazolam Toluene Sulfonate with Propofol in Orthotopic Liver Transplantation

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The objective of the study is to explore the application value of remimazolam toluene sulfonate in orthotopic liver transplantation. A total of 120 patients who underwent orthotopic liver transplantation in our hospital from March 2021 to December 2022 were randomized into intervention group (R group, n=60, remimazolam toluene sulfonate) and control group (C group, n=60, normal saline). For induction of anesthesia, all patients were administrated with propofol intravenously, study drug (0.2 ml/kg), sufentanil and cisatracurium. Intraoperative infusion of propofol and study drug was used to maintain sedation. All patients returned to intensive care unit to continue infusion for sedation after orthotopic liver transplantation. The dose of propofol, cumulative duration of intraoperative hypertension and dose of norepinephrine were significantly less than those in control group, $p<0.05$. At d 1 after surgery, alanine transaminase, aspartate aminotransferase, total bilirubin, direct bilirubin and creatinine in intervention group were significantly lower than those in control group, $p<0.05$; at d 2 after surgery, alanine transaminase, aspartate aminotransferase, total bilirubin, direct bilirubin and creatinine in intervention group were significantly lower than those in control group, $p<0.05$. 3rd after surgery, aspartate aminotransferase in intervention group was significantly lower than that in control group, $p<0.05$. The albumin-bilirubin score, incidences of postoperative early allograft dysfunction and delirium and duration of cannulation were not significantly different among two groups, $p>0.05$. Remimazolam toluene sulfonate can stabilize perioperative hemodynamics and reduce hypertension, thus can be used in liver transplantation and preserve early liver graft function after orthotopic liver transplantation.

Key words: Remimazolam toluene sulfonate, propofol, orthotopic liver transplantation, sufentanil, cisatracurium

Orthotopic Liver Transplantation (OLT) is the only treatment of various end stage liver diseases currently. Intense stress, inflammatory reaction and immune regulatory dysfunction occur in major abdominal surgery. These risk factors may accelerate damage of liver graft function after OLT and lead to adverse prognosis[1]. Previous studies confirmed that Intravenous (IV) anesthetics, such as propofol and midazolam, could relieve Hepatic Ischemia Reperfusion Injury (HIRI) and protect the liver through enhancing antioxidant ability, inhibiting immune function and inflammatory reactions[2]. Remimazolam toluene sulfonate is a novel ultra-short-acting IV anesthetic agent and has similar mechanism of action as midazolam since it's the derivative of midazolam. Quality clinical studies with large sample size are necessary for understanding whether remimazolam toluene sulfonate has liver-protection effect and its safety and efficacy in liver transplantation. The present study included OLT patients as subjects and explored the safety of remimazolam toluene sulfonate in OLT and the preservation of early liver graft function after OLT.

MATERIALS AND METHODS

Subjects and clinical information:

A total of 120 patients who underwent selective OLT in this hospital from March 2021 to December 2022, including 30 males and 90 females, aged (18~25) y and Body Mass Index (BMI) 18.01~29.98

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kg/m^2; American Association of Anesthesiologists (ASA) grade III-IV; preoperative Model for End-stage Liver Disease (MELD) score 6~29. These patients were assigned into intervention group (R, n=60, infusion of remimazolam toluene sulfonate) and control group (C, n=60, infusion of normal saline) by a random number table. The present study was approved by the Ethics Committee of Tsinghua Changgung Hospital (Number: 20384-4-01) and registered in China Clinical Trial Center (Registration Number: ChiCTR2000040583). All patients signed informed consent.

Selection of subjects:

Inclusion criteria: Patients of age (18~65) y; BMI 18~30 kg/m^2; ASA grade II-IV; patients who underwent OLT and signed informed consent were included in the study.

Exclusion criteria: Patients with poor glycemic control before surgery (preoperative glucose≥12 mmol/l or glycated Haemoglobin (HbA1c)>8.5 %); MELD score>30; complicated with severe cardiopulmonary diseases; unstable hemodynamics; preoperative life support (mechanical ventilation and kidney replacement therapy); severe infection; allergy to anesthetic drugs and patient denial, were excluded.

Management of anesthesia:

The staff of anesthesia prepared the drug and patients in the intervention group (R group) were infused with remimazolam toluene sulfonate for injection (Ruibeilin, Hengrui, Jiangsu) which was diluted to 36 ml with normal saline. Patients in control group (C group) were infused with normal saline 36 ml as blank control. The staff who formulated drugs would not participate in perioperative management of patients and any postoperative follow-up.

Peripheral venous access was made for all patients in the surgery room. The 5-lead Electrocardiogram (ECG), Saturation of peripheral Oxygen (SpO_2), Non-Invasive Blood Pressure (NIBP) and Bispectral Index (BIS) were monitored. Radial/brachial artery puncture and catheterization was performed to monitor Arterial Blood Pressure (ABP), Stroke Volume Variation (SVV) and Cardiac Output (CO). For rapid induction of anesthesia, patients were administrated IV with propofol in R group 1.5~2.5 mg/kg, sufentanil 0.3~0.5 μg/kg, cisatracurium 0.3 mg/kg and the study drug 0.2 ml/kg. Visualized endotracheal intubation was performed for intermittent positive pressure ventilation, fraction of inspired oxygen 50 %-60 %, tidal volume 6~8 ml/kg, ventilation frequency 10~12 times/min, inspiratory-to-expiratory 1:1.5 and partial Pressure of End-Tidal Carbon Dioxide ($PETCO_2$) 30~40 mmHg. A 7F triple lumen central venous catheter (Arrow, United States) was placed in internal jugular vein/subclavian vein for continuous infusion and monitoring Central Venous Pressure (CVP). All patients were continuously administrated IV with propofol 4-8 mg/kg/h, study drug 0.3 ml/kg/h, sufentanil 0.25~0.5 μg/kg/h and cisatracurium 1~2 μg/kg/min for maintenance of anesthesia. The dose of propofol was adjusted according to Heart Rate (HR), ABP and BIS of patients during anesthesia. BIS was maintained at 40~60. Intraoperative Mean Arterial Pressure (MAP) was maintained >70 % of baseline and vasoactive agents were used if necessary. The objective of body fluid management was to maintain CVP≤12 cmH_2O and SVV of anhepatic phase and neohepatic phase was maintained at <13 %. All patients used Patient-Controlled IV Analgesia (PCIA, hydromorphone 12 mg+ondansetron 20 mg+normal saline to a volume of 250 ml, background infusion rate 3 ml/h, Patient-Controlled Analgesia (PCA) dose 3 ml, lock time 15 min) until d 3 after surgery.

All patients returned to Intensive Care Unit (ICU) with endotracheal tube for further treatment and continued infusion of propofol 1-4 mg/kg/h and the study drug 0.3 ml/kg/h for sedation. In order to stabilize the patient's blood pressure in the normal range, the appropriate amount of deoxyepinephrine and methoxamine was administered and the dosage was recorded.

Parameters:

Primary observational parameters: The parameters of postoperative functional evaluation of liver graft.

Albumin-Bilirubin (ALBI) score of portal vein access within 72 h was as follows. ALBI score=0.66×l g bilirubin (μmol/l)+(-0.085)×Albumin (ALB, g/l). ALBI grade 1: ≤-2.60; ALBI grade 2: -2.60<ALBI score<-1.39 and ALBI grade 3: ≥-1.39[3].

Alanine Transaminase (ALT), Aspartate

Aminotransferase (AST), ALB, Direct Bilirubin (DBil), Total Bilirubin (TBil), International Normalized Ratio (INR), C-Reactive Protein (CRP) and glucose were detected at T0 (before surgery), T1 (d 1 after surgery), T2 (d 2 after surgery), T3 (d 3 after surgery) and T4 (d 7 after surgery).

Postoperative incidence of Early Allograft Dysfunction (EAD)[4] was as follows, where TBil≥171 μmol/l on d 7, INR≥1.6; AST or ALT>2000 U/l within 7 d after surgery. The patient who had any one of these conditions could be diagnosed.

Secondary observational parameters: Secondary observational parameters were discussed below.

For the analysis of intraoperative hemodynamic stability, it includes the cumulative duration of intraoperative hypotension (MAP), dose of vasoactive agents, fluid intake and output and use of blood products were recorded.

The short-term prognosis parameters include postoperative time to decannulation, days of stay in ICU and hospital stay.

Incidence of postoperative delirium is as follows. The scale of delirium, Confusion Assessment Method for the ICU (CAM-ICU/CAM) was used to evaluate the delirium on d 1-5 after surgery.

Statistical analysis:

Statistical Package for the Social Sciences (SPSS) 26.0 software was used for statistical analysis. Continuous data of normal distribution were expressed by mean±Standard Deviation (SD) ($\bar{x}\pm s$) and analyzed by independent sample t-test; continuous data of non-normal distribution were expressed by median (interquartile range) and analyzed by rank sum test. Enumeration data were expressed by n (%) and analyzed by chi-square test or Fisher's exact test. All statistical tests were two-sided, $p<0.05$ indicated statistical significance.

RESULTS AND DISCUSSION

Preoperative baseline data and laboratory parameters were shown in Table 1. No patients withdrew this study in either group. As shown in Table 1, sex, age, BMI, ASA grade, preoperative MELD score, Child-Pugh score and preoperative laboratory parameters were not significantly different among two groups, $p>0.05$.

TABLE 1: PREOPERATIVE BASELINE DATA AND LABORATORY TESTS USED IN THE STUDY

Parameters	R group (n=60)	C group (n=60)	p
Age (years)	51 (42, 61)	51 (46, 58)	0.823
Sex, n (%)			0.206
Male	42 (70 %)	48 (80 %)	
Female	18 (30 %)	12 (20 %)	
BMI (kg/m^2)	23.56±3.57	24.01±3.15	0.47
ASA grade, n (%)			0.648
III	47 (78.3 %)	49 (81.7 %)	
IV	13 (21.7 %)	11 (18.3 %)	
Preoperative MELD score	17.5 (13.3, 25)	15 (10.3, 22)	0.075
Preoperative Child-Pugh score, n (%)			0.232
A	22 (36.7 %)	27 (45 %)	
B	24 (40 %)	26 (43.3 %)	
C	14 (23.3 %)	7 (11.7 %)	
Preoperative laboratory parameters			
AST (U/l)	38.1 (24.4, 9.9)	32.6 (23.8, 74.0)	0.948
ALT (U/l)	26.8 (17.9, 47.8)	24.9 (15.8, 39.8)	0.358

TBil (μmol/l)	58.4 (22.6, 159.0)	33.4 (15.9, 88.2)	0.225
DBil (μmol/l)	36.1 (11.9, 99.7)	16.3 (7.4, 69.3)	0.206
ALB (g/l)	34.3 (31.3, 37.2)	34.5 (32.3, 38.3)	0.582
INR	1.43 (1.18, 1.66)	1.35 (1.15, 1.67)	0.386
Cre (μmol/l)	54.1 (45.9, 75.5)	60.2 (51.9, 75.1)	0.15
Glucose (mmol/l)	5.51 (4.71, 7.64)	5.98 (4.74, 7.92)	0.7

Perioperative parameters of the study were shown in Table 2. Duration of surgery, anesthesia and anhepatic phase, dose of deoxyepinephrine, methoxamine, propofol and sufentanil, fluid intake, crystalloid liquid, ALB, Red Blood Cell (RBC), infusion dose of plasma, urine volume and blood lose were not significantly different among two groups, $p>0.05$. As shown in Table 2, in comparison with C group, the dose of propofol and norepinephrine in R group were significantly lower and the duration of intraoperative hypotension was significantly less, $p<0.05$.

Postoperative laboratory parameters at different time points were shown in Table 3. ALB, INR and glucose were not significantly different at T1~T4 among two groups, $p>0.05$. As shown in Table 3, at T1, ALT, AST, TBil, DBil and Creatinine (Cre) in R group were significantly lower than those in C group, $p<0.05$; at T2, AST, TBil, DBil and Cre in R group were significantly lower than those in C group, $p<0.05$; at T3, AST in R group was significantly lower than that in C group, $p<0.05$.

Postoperative parameters were shown in Table 4. As shown here, ALBI score within 72 h after portal vein access, incidences of postoperative EAD and delirium, duration of cannulation, stay in ICU and hospital stay were not significantly different among two groups, $p>0.05$.

Lipid peroxidation and mass Reactive Oxygen Species (ROS) in liver transplantation, increased malondialdehyde levels and accelerated oxidative stress response are considered as the main mechanism of HIRI and early liver graft dysfunction[5]. Previous studies reported that oxidative stress and inflammatory reaction may accelerate liver graft dysfunction, while antioxidant stress system could relieve HIRI[6]. Our previous studies showed that significant inflammatory reaction after OLT was associated with adverse prognosis[7,8]. Functional protection of liver graft after OLT is a common objective of perioperative management in both transplantation surgery and anesthesiology department. Previous study showed that common IV anesthetics, such as dexmedetomidine, propofol and midazolam, had the effect of organ protection[9]. Propofol and midazolam have been confirmed to have abilities to eliminate ROS, reduce lipid peroxidation reaction and enhance anti-oxidation, and can protect the liver through improving the oxidative stress response in the liver after ischemia reperfusion.

Remimazolam toluene sulfonate is a derivative of midazolam and has the advantages of short time of action, good controllability and absence of accumulation after long-term infusion in comparison with midazolam. Remimazolam toluene sulfonate has been used in painless gastroscopy, hysteroscopy and bronchoscopy since marketing, and its safety and efficacy have been confirmed[10,11]. However, the application of remimazolam toluene sulfonate in liver transplantation has been less reported. Onoda *et al.* showed that remimazolam had been used in anesthesia management of liver cirrhosis patients[12] and this was consistent with the present study. Matsumoto *et al.*[13] and Kawasaki *et al.*[14] reported that remimazolam could be used in liver transplantation with small fluctuation of perioperative blood flow. The present study showed that propofol combined with remimazolam toluene sulfonate could be used in liver transplantation, reduce the dose of propofol, decrease the incidence of intraoperative hypotension, reduce the use of vasoactive drugs and provide stable hemodynamics. A study of rat model by Fang *et al.*[15] showed that remimazolam could inhibit inflammatory reaction and oxidative oxygen stress in hepatocytes and reduce sepsis associated acute liver injury through inhibiting phosphorylation of p38 in macrophages and activating peripheral benzodiazepine receptor. In the present study, although the ALBI score and the incidence of postoperative EAD were not improved significantly within 72 h after portal

vein access in R group compared with those in C group, abnormal increase of early ALT, AST, TBil and DBil was small, indicating that remimazolam toluene sulfonate could preserve early liver graft function after liver transplantation. The change of perioperative blood flow in the liver is critical for postoperative liver graft function in OLT. In comparison with propofol, remimazolam toluene sulfonate has a smaller effect on hemodynamics, thus can maintain perioperative blood flow in the liver, this may be a mechanism of liver protection. Hemodynamic fluctuation, hypotension and use of vasoactive drugs in liver transplantation are risk factors of postoperative renal insufficiency. In the present study, the duration of intraoperative hypotension was significantly shortened, the use of vasopressor drugs was significantly decreased and early postoperative Cre level was decreased, this may be associated with more perioperative hemodynamics and better renal perfusion. Intraoperative infusion of remimazolam toluene sulfonate didn't increase the incidence of postoperative delirium, duration of cannulation or stay in ICU of patients with liver transplantation.

In conclusion, remimazolam toluene sulfonate can be used in liver transplantation safely. In comparison with propofol alone, propofol along with remimazolam toluene sulfonate can stabilize intraoperative hemodynamics, reduce hypertension, preserve early liver graft function and kidney function after OLT, and doesn't increase the incidence of postoperative delirium or duration of cannulation. However, in the present study, neither postoperative ALBI score nor the incidence of EAD was improved significantly. Quality clinical studies with large sample size are necessary for understanding the liver-protection effect of remimazolam toluene sulfonate and the mechanism, whether high dose and long term IV infusion can increase the time of recovery after major surgery and the incidence of delirium.

TABLE 2: PERIOPERATIVE PARAMETERS OF THE STUDY

Parameters	R group (n=60)	C group (n=60)	p
Duration of surgery (h)	9.33 (8.02, 10.45)	8.84 (8.06, 10.22)	0.475
Duration of anesthesia (h)	10.83 (9.62, 12.05)	10.38 (9.44, 11.82)	0.669
Anhepatic phase (min)	58 (46, 70)	62 (54, 70)	0.07
Duration of intraoperative hypotension (min)	12 (9, 18)	20 (13, 34)	<0.001*
Vasoactive drugs (mg)			
Dose of deoxyepinephrine	0.30 (0.08, 0.47)	0.26 (0.12, 0.40)	0.591
Dose of methoxamine	29.3 (10.4, 39.5)	25.9 (9.5, 49.3)	0.610
Dose of norepinephrine	0.67 (0.20, 1.65)	1.23 (0.53, 2.19)	0.016*
Dose of remimazolam toluene sulfonate (mg)	125 (88.8, 144.0)	--	--
Dose of propofol (mg)	2296.0±846.7	3030.6±942.9	<0.001*
Dose of sufentanil (mg)	148 (135.5, 172.3)	161.2 (150.8,179.5)	0.354
Fluid intake (ml)	5675 (4813, 6200)	5950 (5046, 6840)	0.083
Crystalloid liquid (ml)	3475 (2850, 3988)	3775 (3025, 4588)	0.105
ALB (ml)	1850 (1550, 2400)	1950 (1700, 2400)	0.491
RBC (U)	2 (0, 4)	1.5 (0, 4)	0.854
Plasma (ml)	250 (0, 400)	100 (0, 400)	0.825
Urine (ml)	1080 (778, 1845)	1200 (705, 1789)	0.797
Blood loss (ml)	400 (200, 500)	400 (200, 600)	0.858

Note: *p<0.05, results were expressed as mean±SD or median (interquartile range) or n (%). Duration of intraoperative hypotension is cumulative duration of MAP<60 mmHg

TABLE 3: POSTOPERATIVE LABORATORY PARAMETERS AT DIFFERENT TIME POINTS

Parameters	R group (n=60)	C group (n=60)	p
ALBI score within 72 h after portal vein access	-2.04±0.32	-2.00±0.30	0.530
ALBI grade, n (%) 1 2 3	 0 59 (98.3 %) 1 (1.7 %)	 2 (3.3 %) 54 (90 %) 4 (6.7 %)	0.134
Incidence of postoperative delirium, n (%)	11 (18.3 %)	9 (15 %)	0.624
Postoperative duration of cannulation (min)	410 (243, 798)	335 (205, 906)	0.253
Stay in ICU (d)	6 (5,7)	6 (5,7)	0.451
Postoperative hospital stay (d)	21 (17, 29)	20 (17, 25)	0.299
Postoperative EAD, n (%)	5 (8.3 %)	2 (3.3 %)	0.243

TABLE 4: POSTOPERATIVE PARAMETERS OF THE STUDY

Laboratory parameters	Group	n	Postoperative			
			T1 (d 1)	T2 (d 2)	T3 (d 3)	T4 (d 4)
ALT (U/l)	R	60	433.0 (218.6, 569.3)	363.2 (207.9, 539.0)	242.8 (145.9, 382.0)	63.6 (44.4, 138.3)
	C	60	518.7 (298.3, 843.3)	285.2 (168.3, 418.7)	201.6 (119.8, 325.6)	85.5 (39.4, 127.1)
	p		0.031*	0.128	0.214	0.631
AST (U/l)	R	60	567.6 (404.2, 848.9)	135.1 (78.7, 227.3)	62.6 (41.9, 95.6)	19.4 (13.9, 33.4)
	C	60	704.1 (470.6, 1177.1)	172.6 (112.5, 263.6)	78.7 (56.5, 114.0)	19.0 (13.9, 33.1)
	p		0.044*	0.008*	0.047*	0.741
TBIL (μmol/l)	R	60	56.5 (37.8, 102.0)	27.2 (15.8, 56.0)	25.1 (15.5, 55.1)	23.1 (15.9, 46.3)
	C	60	75.8 (48.3, 156.4)	42.0 (18.1, 98.5)	31.1 (16.3, 48.5)	22.0 (13.9, 42.7)
	p		0.038*	0.041*	0.777	0.342
DBil (μmol/l)	R	60	47.2 (28.8, 74.9)	19.4 (13.4, 39.9)	18.6 (10.4, 43.5)	14.8 (9.8, 34.6)
	C	60	59.6 (39.9, 133.4)	31.9 (13.8, 83.4)	20.3 (12.8, 39.2)	14.0 (7.9, 31.7)
	p		0.029*	0.04*	0.84	0.305
ALB (g/l)	R	60	35.2 (32.6, 38.5)	33.8 (31.7, 36.0)	35.3 (33.2, 37.7)	32.9 (31.7, 34.7)
	C	60	35.6 (33.1, 38.4)	34.5 (33.1, 36.0)	34.7 (33.2, 36.3)	34.0 (31.3, 35.3)
	p		0.755	0.194	0.364	0.333
INR	R	60	2.25 (1.91, 2.76)	1.36 (1.24, 1.55)	1.17 (1.10, 1.31)	1.08 (1.01, 1.15)
	C	60	2.18 (1.83, 2.74)	1.32 (1.20, 1.56)	1.16 (1.05, 1.32)	1.06 (0.98, 1.19)

		p	0.56	0.469	0.436	0.99
Cre (μmol/l)	R	60	67.3 (56.7, 77.8)	67.5 (54.5, 80.5)	66.0 (48.3, 82.8)	57.5 (45.0, 78.5)
	C	60	79.5 (59.0, 95.0)	76.5 (58.6, 106.3)	68.2 (54.7, 97.5)	63.0 (49.0, 78.2)
		p	0.033*	0.021*	0.144	0.148
Glucose (mmol/l)	R	60	9.4 (8.0, 10.9)	8.3 (7.5, 9.1)	8.3 (7.0, 9.9)	6.1 (5.2, 7.7)
	C	60	9.1 (7.4, 10.8)	8.4 (7.5, 9.7)	8.0 (6.7, 9.7)	6.0 (5.1, 7.2)
		p	0.462	0.442	0.402	0.495

Note: *p<0.05, results were expressed as mean±SD or median (interquartile range) or n (%)

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Conflict of interests:

The authors declared no conflict of interest.

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