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Original Article

Pharmacodynamics of cisatracurium in adults and children undergoing living donor liver transplantation

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Abstract: This study aims to investigate the pharmacodynamics of bolus administration of cisatracurium in adults and children undergoing living donor liver transplantation. Forty-two patients (ASA III) undergoing living donor liver transplantation were assigned to group A (21 adults) or group B (21 children affected by congenital biliary atresia). All patients received a 2 fold ED_{95} of cisatracurium (0.1 mg/kg) to facilitate the tracheal intubation and neuromuscular blocking was monitored by train-of-four. An additional dose of cisatracurium (0.03 mg/kg) was given once T1 recovered to 25% or 4 train-of-four (TOF) responses observed. Cisatracurium administration and sevoflurane inhalation were stopped in pre-anhepatic phase, anhepatic phase, and after portal reperfusion, but recontinued when T1 recovered to 75%. The delivery interval and recovery of muscular blockade were recorded. The onset time of cisatracurium was significantly shorter in adults, however, it did not show any difference to facilitate the tracheal intubation between adults and children undergoing living donor liver transplantation Children in group B experienced significantly higher incidence of metabolic acidosis, cholestasis, hyperlactacidemia and cellular destruction. The delivery interval and the duration of cisatracurium within these three phases were similar for adult or children the recovery index in group B was significantly lower than that in group B In conclusion, a 2 × ED_{95} dose of cisatracurium can provide a favorable condition for tracheal intubation for either adult or children undergoing living donor liver transplantation. However, children usually have a significantly longer onset time and a shorter recovery time the interval of the cisatracurium administration does not change with age.

Keywords: Cisatracurium, living donor liver transplantation, congenital biliary atresia, pharmacodynamics, train of four (TOF)

Introduction

Liver transplantation (LT), which is considered as the only effective option for saving patients suffering from end-stage liver disease, has been widely performed With the improvement of surgical technique and perioperative management, the one-year survival rate after liver transplantation has increased from 30% in the 1870s to 90% now actually [1]. The five-year survival rate is over 80% [2] for now. According to a census report, the number of patients waiting for liver transplantation in the United States in the year of 2012 has exceeded 17,000. Among them, children account for approximately 15%-20%. In addition, over two-thirds of the infant patients were younger than 5 years old [3]. Patients younger than 5 years old and affected by end-stage liver diseases differ greatly from adult patients with regard to etiology, surgical procedures, perioperative management, and pharmacodynamics or pharmacokinetics of anesthetics [4]. Moreover, the postoperative mortality rate is much higher for children with end-stage liver disease undergoing liver transplantation than those from any other age groups. On the other hand, for now there is no guidance of perioperative management for child patients under 5 years old experiencing liver transplantation. Therefore, it is of great importance to make a consensus or guidance to optimize perioperative management and potentially to improve the survival rate

Congenital biliary atresia (CBA) is a congenital disease of obscure etiology and itis also the most common cause of chronic cholestasis in infants and young children. The mortality rate

within 2 years after birth is almost 100% for untreated patients. A great part of children receive Kasai procedure which is characterized by hepaticojejunostomy at an early stage, however, biliary obstruction cannot be completely resolved with Kasai surgery and the liver becomes cirrhotic in several months [5].

According to the annual scientific report of Chinese pediatric liver transplantation published in 2011 [6], there were 337 cases of pediatric liver transplantation registered from 1993 to 2011 and CBA accounted for 49.3% in 2008 and 54.2% in 2009.

Patients usually undergo severe hemodynamic and pathophysiological instabilities in liver transplantation. The specific surgical procedure comprising pre-anhepatic, anhepatic, and neohepatic phases is technically complicated and time-consuming. Furthermore, there is no published consensus or evidence to guide the perioperative management for these patients. Pharmacikinetics and pharmacodynamics of anesthetics may differ from healthy adults and an optimized individual medication strategy is warranted to improve the recovery.

Cisatracurium besylate is a non-depolarizing neuromuscular blocking drug and is very similar to atracurium besylate with regard to the metablic pattern. It is about 3-fold more effective than atracurium without releasing histamine or cardiovascular depressing profile. Cisatracurium undergoes spontaneous degradation, which makes it an ideal neuromuscular blocking agent for patients complicated with liver or renal disease [7]. Evidence showed that cisatracurium could be used perioperatively for pediatric patients [8-10], especially for those complicated with chronic liver disease [11]. However, there is very limited studies investigating the pharmacodynamics of cisatracurium in pediatric liver transplantation, especially for infants under 1 year old [7, 12, 13].

Therefore, our study basically was designed to investigate the pharmacodynamics of cisatracurium besylate in adults and children with end stage liver disease and undergoing living donor liver transplantation and to see whether cisatracurium is suitable to be used in child patients younger than 1 year old who receiving living donor liver transplantation.

Methods

Patients

After the approval of the ethics committee of Shanghai Renji Hospital, informed consent was signed by the patient or their legal guardian. In this prospective observational study, 42 patients (ASA II-III) undergoing adult-adult or adult-pediatric living donor liver transplantation in Renji Hospital, Shanghai Jiaotong University School of medicine from May 2008 to December 2010 were assigned into two groups. 21 adult patients were included in group A, all patients were affected by end stage liver disease and the etiology included viral hepatitis (n=13), primary hepatic cancer (n=5) and autoimmune liver disease (n=3). 21 child patients were included in group B. They were all affected by cogenital biliary atresia (CBA). The morphometric and demographic details of both groups are noted. The exclusion criteria: any history of neuromuscular disorders, morbid obesity(body mass index [BMI] $\geq$ 30 kg/m^2), severe hepatic encephalopathy, history of liver transplantation, psychological disorder or cogenital malformations. All the liver donors were relatives of the recipients, including parentage (22/42), sibling, collateral relatives (15/42) and grandparent (1/42). Informed consent of all donors were also obtained. The surgical procedure of all of the patients included in our study is living donor liver transplantation.

Operation

All patients were routinely prepared before surgery, including liver and renal tests, blood gas analysis, electrolyte test, coagulation test etc. Adult patients were fasted for 12 h preoperatively and intramuscularly injected with phenobarbital 0.1 g and atropine 0.5 mg 1 h as premedication. Patients in group B were fasted for 6 h before surgery as well as deprived of water for 3 h prior to the operation, they were premedicated with ketamine 4-6 mg/kg and atropine 0.01-0.02 mg/kg.

All patients were routinely monitored: electrocardiogram (ECG), heart rate (HR), blood pressure (BO) and pulse oximetry (SpO_2). In group A, the intravenous perfusion was achieved with a catheter (22G) in the left back of the hand. An invasive arterial blood pressure was monitored via radial artery catheterization under

local anesthesia. The anesthesia was inducted with midazolam 0.05 mg/kg, fentanyl 3-5 μg/kg, propofol TCI (targeted concentration infusion) 3 μg/ml and cistracurium (Glaxo Smith-Kline, Middlesex UK, European production line) 0.1 mg/kg. Endotracheal intubation was performed once the neuromuscular blockade achieved. The anesthesia was maintained with sevoflurane (1 MAC) and fentanyl (1-2 μg/kg hourly) and the mechanical ventilation was optimized to maintain an $EtCO_2$ between 35 mmH_2O and 45 mmH_2O. An arterial blood was sampled through the radial arterial catheter for blood gas analysis and electrolyte testing after endotracheal intubation, 5 min before anhepatic phase, 15 min after anhepatic phase, 5 min and 30 min after portal refersuion in order to optimize an homeostasis. In group B, a premedication with ketamine 4-6 mg/kg and atropine 0.01-0.02 mg/kg were performed about 5 min before entering the operating room. An intravenous catheter (24 G) was inserted into the left hand or arm and an infusion of 5% glucose was slowly started. The induction was achieved with the same dosage as in group A. An endotracheal tube was carefully inserted with a laryngoscope and was properly fixed before auscultation. Anesthesia was maintained with sevoflurane (1 MAC) and fentanyl as the same dosage of adults in group A. An invasive BP monitoring and the blood gas analysis were done at the same time points as in group A.

All patients were inserted with a PiCCO catheter (PULSION Medical Systems SE, Germany) through the femoral artery for monitoring the cardiac output and the core temperature. Fluids was perfused with a warming device and an insulation blanket was placed to ensuring a body temperature between 36.4 and 37.4°C during the surgery and a body temperature ≥ 35°C in the first 10 min of new liver perfusion as reported in another study [14]. The urinary output was monitored and diurese was used as need to maintain an urine volume > 1 ml/kg/h. Once anhepatic began, patients in group A received an intravenous or intramuscular injection of human hepatitis B immune globulin and methylprednisolone was administered before portal reperfusion.

All patients were placed with a TOF-Watch SX accelerometer (Organon, Ireland, Ltd.) to monitor the muscle twitch responses of the adductor pollicis. The surface electrode was pasted on the ulnar side of the left forearm proximal to the wrist to stimulate the ulnar nerve. The negative electrode was placed on the radial side of the intersection of the flexor carpi ulnaris and proximal rasceta. The positive electrode was placed 2-3 cm above (mesial end of) the negative electrode. The acceleration sensor was fixed on the palm side of the distal knuckle of the thumb. The transducer was placed vertical to the direction of thumb movement. The temperature probe was fixed on the skin of the thenar eminence. The upper arm and forearm were partially insulated to keep the skin temperature of the thenar eminence and palm higher than 32°C [14]. A train-of-four (TOF) stimulation was started before induction to have a figure of baseline and after T1 was stable (90%-110%) for 3 min, induction with 2 × ED_{95} dose (0.1 mg/kg) of cisatracurium was started. The endotracheal intubation was performed once the maximal blockade of T1 was achieved. Muscle relaxation was monitored perioperatively and when T1 recovered to 25% of the control value or 4 TOF responses occurred, an additional 0.03 mg/kg of cisatracurium was delivered. The administration of cisatracurium was stopped and sevoflurane was adjusted to under 1 MAC just after the clamping of portal vein (anhepatic phase) and after the portal reperfusion (neohepatic phase). The revocery of neuromuscular blockade was monitored, and muscle relaxants and inhalation anesthesia were readministered again when T1 reached 75%. The onset time of blockade (from the end of the intravenous injection of cisatracurium to the time of the maximum T1 blockade), intraoperative dosing interval (when T1 recovered to 25% or 4 TOF responses appeared on screen, the interval of a super addition of 0.03 mg/kg of cisatracurium), clinically effective duration of neuromuscular blocking effect (from the maximum blockade of T1 to 25%) and recovery index (RI) (the duration of T1 recovery from 25% to 75%) were recorded. We have also evaluated the condition of endotracheal intubation by using a 1-4 scale based on ease of laryngoscopy, position of vocal cords, degree of coughing and jaw relaxation. A score of 3-4 was considered excellent; 5-8, good; 9-12, poor; and 13-16, bad. Excellent and good scores were considered as clinically acceptable, and fair and poor scores were considered as clinically unacceptable [*tracheal intubation without neu-*

Table 1. General information of both groups

General Information	Group A	Group B
Age (year)	44.10 ± 10.87	0.98 ± 0.40▲
Body weight (kg)	64.05 ± 7.74	8.12 ± 1.54
Gender (M/F)	15/6	14/7
BMI (kg/m^2)	22.94 ± 2.45	-[a]
Standard body weight of children (kg)	-	9.66 ± 1.20*
Operation time (min)	552.67 ± 69.34	483.14 ± 83.44▲
Anesthesia time (min)	639.24 ± 70.60	629.62 ± 79.46

▲$P < 0.05$ compared with group A; *$P < 0.05$ compared with the standard body weight of the same age. [a]Data were not properly collected, and relevant features were assessed according to the reference standard released by China's Maternal and Children Health Care and Community Health Division.

Table 2. Preoperative blood tests

Biochemical indicators	Group A	Group B	Normal reference ranges
Hb (g/l)	101.81 ± 24.60	69.56 ± 23.40▲	113-151
WBC (*10^9/l)	3.84 ± 2.15	8.79 ± 6.61▲	3.69-9.16
Plt (*10^9/l)	61.90 ± 39.21	146.00 ± 94.33▲	101-320
Cr (μmol/l)	84.33 ± 55.71	16.08 ± 7.11▲	45-104
γ-GT (U/l)	77.35 ± 97.02	272.15 ± 291.00▲	7-32
AST (U/l)	99.43 ± 90.99	339.76 ± 201.62▲	10-28
ALT (IU/l)	60.95 ± 57.05	199.48 ± 185.21▲	0-75
Alb (g/l)	36.01 ± 5.33	30.30 ± 6.87▲	34-54
A/G	1.26 ± 0.30	1.02 ± 0.24▲	1.25-2.00
SB (μmol/l)	155.55 ± 144.48	162.62 ± 101.04	0.1-5.0
TB (μmol/l)	429.68 ± 410.79	300.36 ± 188.61	3.4-17.1
PT (s)	26.56 ± 16.24	21.43 ± 8.09	9.4-12.5
INR	2.23 ± 1.26	1.95 ± 0.81	0.8-1.15

▲$P < 0.05$ compared with group A.

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Statistics

Data were analyzed with SPSS 13.0 statistical software and the significance level was set at $P < 0.05$. The results were reported as mean ± standard deviation if normal distribution was met. These data met the requirement of Huynh-Feldt and were analyzed by one-way ANOVA. Repeated measurement data were analyzed using ANOVA. The comparison of measurement data between two groups were performed using one-way ANOVA. Enumeration data were analyzed using the Chi-square test.

Results

The morphometric and demographic data is presented in **Table 1**: age and body weight are significantly different between two groups since we have included adult patients in group A and pediatric patients in group B ($P < 0.05$). However, there is no difference in gender composition. The mean age of the patients in group B was 11.62 ± 4.94 months, and their body weight was 8.12 ± 1.54 kg, which was significantly lower than the referenced standard weight of children at the same age, which should be 9.66 ± 1.20 kg ($P < 0.05$), published by China's Maternal and Children Health Care and Community Health Division, Ministry of Health, in September 2009. The surgical duration of group A is shorter than that in group B ($P < 0.05$), while there was no significant difference with respect to the duration of anesthesia (**Table 1**). Routine blood tests were performed before surgery and the results (**Table 2**) showed that patients in group B experienced significantly higher prevalence of anemia ($P < 0.05$). White blood cell counts were significantly different between the two groups of patients ($P < 0.05$). However, the values were within the normal range. Patients in group A had significantly higher prevalence of thrombocytopenia compared with group B ($P < 0.05$). The average serum creatinine level was within the normal range in group A, while it was significantly lower than the normal level in group B ($P < 0.05$). γ-glutamyltransferase (γ-GT), aspartate transaminase (AST), and alanine aminotransferase (ALT) levels were dramatically high in both of the groups. Moreover, γ-GT, AST, and ALT levels were significantly higher in group B compared with that in group A ($P < 0.05$). The serum albumin level and albumin/globulin ratio in group B were lower than the reference values, as well as those in group A ($P < 0.05$). There was no statistically significant difference in direct bilirubin, total bilirubin, prothrombin time, and international normalization ratio (INR) between these two groups.

Table 3. The onset time of cisatracurium in these two groups

Onset	Group A	Group B
Onset time (s)	336.43 ± 46.37	537.14 ± 96.00▲
Intubation condition (favorable/unfavorable)	19/2	20/1
Intubation satisfaction degree (%)	90.48	95.24

▲$P < 0.05$ compared with group A.

Table 4. Arterial blood gas analysis after intubation

Biochemical indicators	Group A	Group B	Normal reference ranges
pH	7.40 ± 0.69	7.28 ± 0.09▲	7.35-7.45
pCO_2 (mmHg)	35.26 ± 3.42	44.80 ± 8.47▲	32.0-48.0
pO_2 (mmHg)	413.86 ± 60.76	302.43 ± 97.64▲	83.0-108
BE (mmol/l)	-1.03 ± 4.22	-5.37 ± 3.09▲	-3-+3
K+ (mmol/l)	3.50 ± 0.80	3.44 ± 0.52	3.5-5.0
Lac	1.00 ± 0.33	1.35 ± 0.39▲	0.5-1.6

▲$P < 0.05$ compared with group A.

After the administration of cisatracurium, four cases in group A and five cases in group B did not meet 100% of T1 blockade. The onset time was significantly shorter in group B compared with group A ($P < 0.05$) (**Table 3**). The degree of intubation satisfaction in both groups of patients were 90.48% and 95.24% respectively (**Table 3**), but without significant difference between two groups ($P > 0.05$) (**Table 3**).

Radial arterial blood gas analysis was done perioperatively (**Table 4**) andmetabolic acidosis was significantly more common in group B ($P < 0.05$) compared with that in group B. Patients in group B had a higher prevalence of hypokaliemia than in group A, but without statistical significance ($P > 0.05$). The lactate level in group B was higher than than that in group A ($P < 0.05$).

Additional administrations of cisatracurium were performed because of the long surgical duration. It was administered twice in the anhepatic phase and approximately 10 times in both the pre-anhepatic and neohepatic phases. We have compared the mean value of the delivery interval in these three phases, however no significant difference ($P > 0.05$) was observed (**Table 5**). In addition, the clinically effective duration of muscle relaxation in the three phases of both groups was comparative and no significant differences were observed (**Table 5**).

There was no significant difference in Recovery index between these three phases within each group ($P > 0.05$), while in each of the three phases, the recovery index was lower in group B than that in group A ($P < 0.05$) (**Figure 1**).

Discussion

Pharmacodynamics and pharmacokinetics of neuromuscular blocking agents may be altered with physiological or pathological settings, affecting the onset, potency or duration of neuromuscular blocking effect [9, 15]. Liver plays a critical role in the metabolism and degradation of most drugs, including muscle relaxants. Therefore, it is essential to optimize the perioperative use of neuromuscular blocking for patients with chronic liver disease, hepatic failure as well as CBA, especially for those undergoing living donor liver transplantation [7].

The neuromuscular potency of cisatracurium is approximately t3-fold that of atracurium. The in vivo degradation of cisatracurium is independent of hepatic and renal function and 80% of the drug is degraded through the Hofmann pathway. N-methyl tetrahydropapaverine (laudanosine) is a degradation metabolite of cisatracurium by Hofmann pathway, which presents at 1/3 as the concentration of the metabolite of atracurium. Cisatracurium has almost no hemodynamic effects, which makes it an ideal neuromuscular blocking agent major surgeries, such as living donor liver transplantation [7, 9, 16, 17].

In clinical practice, an intravenous bolus of up to 2 to 8 fold ED_{95} dose of cisatracurium does not cause histamine release or significant hemodynamic change andit is safe for the elderly, children, patients in the intensive care unit (ICU), as well as for patients with hepatic and renal disease [8, 9, 18]. A previous study demonstrated that the ED_{95} of cisatracurium is 0.05 mg/kg in adults [19]. Other research revealed that the ED_{95} of cisatracurium was 0.047 mg/kg in children under halothane anesthesia [20]. Endotracheal intubation is usually

Table 5. Intraoperative administration and muscle relaxation duration of cisatracurium

Term indicators	Operation phase	Group A	Group B
Intraoperative administration interval	Pre-anhepatic phase (min)	22.34 ± 3.82	21.57 ± 2.89
	Anhepatic phase (min)	20.93 ± 4.04	20.08 ± 5.20
	Neohepatic phase (min)	21.18 ± 2.97	22.35 ± 5.32
Clinically effective duration of muscle relaxation	Pre-anhepatic phase (min)	20.43 ± 2.79	21.43 ± 7.75
	Anhepatic phase (min)	20.33 ± 4.60	21.71 ± 7.18
	Neohepatic phase (min)	21.14 ± 5.26	19.81 ± 7.15

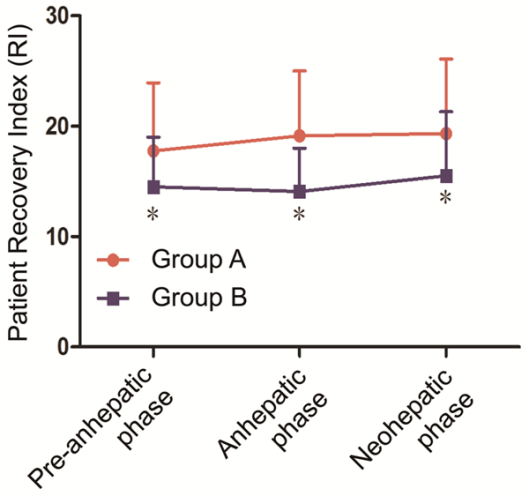

Figure 1. Comparison of the recovery index (RI) between the two groups. *P < 0.05 compared with group A in each phase.

facilitated with a 2 × ED_{95}, which usually offers a satisfying intubation condition [19-22]. Therefore, we have chosen a 2 × ED_{95} dose (0.1 mg/kg) of cisatracurium for induction in this study. According to its pharmacokinetic characteristics, additional administration 1/2 ED_{95} each time) of cisatracurium is feasible for intraoperative maintenance [23]. In our study, we set a dose of 0.03 mg/kg for each additional administration consistenting with the above-mentioned study. Ortiz Gomez et al [24]. reported that 1.3 MAC of sevoflurane for inhalation anesthesia did not significantly affect the recovery index of cisatracurium, thereforewe administered 1.0 MAC of sevoflurane for the maintenance of anesthesia, and we stopped or decrease the inhalation anesthesia (not less than 0.5 MAC) each time we discontinued cisatracurium to minimize the muscle relaxation effect of inhalation anesthesia and to record the recovery time of neuromuscular blocking of cisatracurium.

In our study, the onset time in adult patients was 336.43 ± 46.37 s after intravenous injection of cisatracurium, longer than that reported in healthy adults [17], but shorter than that in patients with severe sepsis [25]. Patients with end-stage liver disease are usually complicated with hypoalbuminemia, tissue edema, and massive ascites, which increase the distribution volume at the steady state (Vdss) of cisatracurium by approximately 20% compared with that in healthy people. These conditions also lead to the reduced distribution of drugs at the neuromuscular junction. It is discussed that in patients with chronic liver disease, the ED_{95} of cisatracurium should be 73.6 μg/kg according to the dose-response curve. All of these factors are likely causing delayed onset of neuromuscular blocking effect of cisatracurium in patients of group A. Clinical studies have proved that the onset of cisatracurium is faster in children than in adults. The onset time was shorter than 5 min in infants, toddlers, and children after the administration of a 2 × ED_{95} dose of cisatracurium [22, 23, 26]. Moreover, the onset was even faster in infants and children than in adolescents who received the same dose [8, 27]. In the present study, the onset time was 537.14 ± 96.00 s in group B, which is significantly longer than that observed in group A and inconsistent with reported study. There are possible explanations: Firstly, all infant patients had different degrees of growth retardation and the actual body weight was significantly lower than the ideal or referenced body weight calculated by months of age. Consequently, the dose for induction according to the actual body weight was significantly lower and results in a prolonged onset of muscle relaxants [28]. Secondly, these children were also affected by anemia, hypoproteinemia, and ascites. Edema and sodium retention can significantly increase the volume of drug distribution. Cisatracurium is a hydrosoluble drug and is primarily distrib-

uted throughout the extracellular fluid. The concentration of muscular relaxant at neuromuscular junctions would be reduced in cases of ascites, which delays the onset [7, 25, 29]. In addition, the changes in plasma pH can also affect the potency and effect of cisatracurium [9, 30, 31]. In our study, the children in group B had significant higher prevalence of metabolic acidosis compared with those patients in group A, which can also explain the delayed onset of cisatracurium in group B. In our study, induction with cisatracurium at 0.1 mg/kg can offer a reliable and satisfying intubation condition, which is consistent with reported evidences [18, 22, 26, 29].

It is reported thatcontinuous use of atracurium for 22.5-98.4 h after pediatric liver transplantationdoes not cause significant accumulation muscle relaxation [13]. Miller et al had infused cisatracurium continuously for up to 3.5 h and no accumulation effects was observed [32]. In addition, the long-term use of cisatracurium in children hospitalized in ICUs had not any effects on the recovery time [12]. In our study, the intraoperative delivery interval of cisatracurium was comparable in these three phases of these two groups. For all patients in our study, the duration of repeated administration of cisatracurium was over 7 h, indicating that it does not result in significant accumulation effects in patients with hepatic failure undergoing living donor liver transplantation and additional administration at constant interval is needed, which is consistent with the reported study.

The clinical effective duration of muscle relaxation in these three phases of both groups was 19.81-21.71 min. The difference was not statistically significant within each group or between the two groups. We have regularly delivered a 1/2 ED_{95} dose (0.025 mg/kg) of cisatracurium and analyzed the means of the clinical duration. The results showed that this dose yielded a clinical effect of shorter duration than the single dose of cisatracurium as reported in some studies [8, 23, 29]. Both hypothermia and acidosis can impact the elimination rate of cisatracurium through the Hoffman pathway [9, 10, 30]. In this study, after the first blood gas analysis, we adjusted the parameters of mechanical ventilation to maintain a PaO_2 level greater than 100 mmHg and a $PaCO_2$ at 35-45 mmHg. We have also infused sodium bicarbonate and diuretics to maintain a pH in the normal range and to prevent the influence of acidosis on muscle relaxation. Moreover, we have combined sustained insulation and active heating and monitored the patients' body temperature to ensure that the core temperature was above 36°C and the peripheral temperature was above 32°C to reduce the interference of temperature on muscle relaxation. Previous work has shown that approximately 16% of the cisatracurium is excreted as prototype in the urine. In the present study, we appropriately used diuretics to keep the urine output greater than 1 ml/kg/h in each phase of the surgical procedure to reduce the impact of the above factors on muscle relaxation effect of cisatracurium [33].

Previous studies reported that when sevoflurane was inhaled at 1.5 MAC, the recovery index of cisatracurium was approximately 19 ± 8 min in adults after administration of 0.1 mg/kg [34]. Other study has also showed that when the concentration of sevoflurane inhaled was maintained at 1.3 MAC, the recovery index of cisatracurium was approximately 14.38 min in adults after administration of 0.1 mg/kg [19]. In adult patients undergoing liver transplantation, the recovery index was 15.4 s after 0.5% isoflurane inhaled and 0.1 mg/kg cisatracurium administered [34]. In this study, 1MAC of sevoflurane was inhaled for anesthesia maintenance to avoid the influence of high concentrations of inhaled anesthetics on neuromuscular effects [35]. In group A, the recovery index in these three phases was consistent with the reported studies. In group B, the intraoperative recovery index was 14.09-15.52 min, similar to the indexes obtained after repeated dosing in other studies [36]. However, the recovery index was longer than that after a single dose in some reports [22, 23, 27]. There are possible explanations: the dose was calculated according to actual body weight and it was significantly lower in group B since children in this group were retarded in development. Moreover, hypoalbuminemia and tissue edema can also lead to an increased volume of drug distribution [7, 29]. The recovery of muscle relaxation of cisatracurium is faster in infants and young children than in adult patients, which may be related to the higher ratio of extracellular fluid to body weight in these patients. Since the dosing of cisatracurium was calculated according to body weight, the plasma concentration of free cisa-

tracurium may be low. In addition, compared with adults, children's heart rate is much faster, therefore blood circulation cycles are shorter and cardiac outputs are higher, which leads to faster clearance and a more rapid recovery of muscle relaxation [21, 27].

In conclusion, a 2 × ED_{95} dose of cisatracurium is a safe and effective choice of neuromuscular blocking agent for anesthesia for both adults and children with hepatic disease and it can also offer a favorable condition for endotracheal intubation the onset was relatively shorterin infants than in adults, but the dosing interval was comparable to that in adults. After discontinuation, infant patients recovered faster than the adult patients. No effect of accumulation effects was observed after after repeated administration for up to 7 h. Therefore, cisatracurium is an ideal muscle relaxant with stable onset, rapid recovery, and no accumulation effect for both pediatric and adult patients undergoing living donor liver transplantation. There is also some limitations in our study, for example: we have not monitored the plasma concentration of cisatracurium or use other administration methods such as continuous infusion to obtain pharmacokinetic data. So, further studies are warranted.

Conclusions

A 2 × ED_{95} dose of cisatracurium can provide favorable conditions for tracheal intubation for both infant and adult patients undergoing living donor liver transplantation and the onset time was longer and the recovery time was shorter in children, but without significant muscle relaxation accumulation.

Disclosure of conflict of interest

None.

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