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Original Article

Sugammadex for Fast-Track Surgery in Children Undergoing Cardiac Surgery: A Randomized Controlled Study

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Objective: The purpose of this study was to evaluate the safety and efficacy of sugammadex for fast-track surgery in children undergoing cardiac surgery.

Design: This was a prospective, randomized, controlled clinical study.

Setting: University hospital.

Participants: The study comprised 60 children undergoing cardiac surgery.

Interventions: The children in group S received sugammadex, 4 mg/kg, for reversal of neuromuscular block, and the children in group N received neostigmine, 30 μg/kg, and atropine, 15 μg/kg.

Measurements and Main Results: The recovery time to a train-of-four of 0.9 and extubation time were significantly shorter in the group S than in group N (3.4 ± 1.2 min *v* 76.2 ± 20.5 min and 31.0 ± 6.4 min *v* 125.2 ± 21.6 min, respectively; $p < 0.01$). The heart rate after drug administration was higher in group S than in group N (102.7 ± 9.4 beats/min *v* 96.9 ± 8.5 beats/min; $p = 0.03$), whereas the mean arterial pressure after drug administration was similar in both groups. The length of hospital stay was shorter in group S (5.8 ± 1.0 *v* 6.5 ± 0.9 days; $p = 0.03$), and the hospitalization expenses were decreased in group S compared with that of group N ($1,036 ± $114 *v* $1,286 ± $187; $p < 0.01$). The incidence of postoperative atelectasis was less in group S than in group N (0 *v* 20%; $p = 0.024$).

Conclusion: Sugammadex can shorten the extubation time and reduce the incidence of postoperative atelectasis, with fewer adverse events, in children undergoing cardiac surgery. It may be beneficial to use sugammadex for fast-track surgery in children undergoing cardiac surgery.

THE CONCEPT of fast-track cardiac surgery is early extubation, mobilization, and hospital discharge in an effort to decrease hospitalization costs and postoperative complications.[1] With the development of fast-track cardiac surgery, fast-track anesthesia is used widely for children undergoing cardiac surgery.[2-5] Fast-track anesthesia is a technique that enables extubation within 6 hours postoperatively.[6] An early extubation is effective and safe in pediatric fast-track cardiac anesthesia without increasing postoperative complications. It facilitates the recovery of spontaneous breathing and reduces postoperative pulmonary complications in children undergoing cardiac surgery.[4] Recently, low-dose and short-acting opioids replaced high-dose opioids in fast-track anesthesia to reduce the length of mechanical ventilation.[7] Recent reports indicated that sugammadex can rapidly reverse the neuromuscular block induced by steroidal nondepolarizing muscle relaxants and shorten the extubation time.[8,9] Sugammadex has allowed for a safer and faster recovery in fast-track bariatric surgery.[10] However, it is unknown whether sugammadex can be used for early extubation and reducing postoperative pulmonary complications in fast-track cardiac surgery. The present study investigated the effects of sugammadex for fast-track surgery in children undergoing cardiac surgery (note: currently the US Food and Drug Administration has not approved the use of sugammadex in children).

Materials and Methods

The present study was approved by the ethics committee of Shanghai Children's Hospital (scmcirb-k2018086). Written

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1053-0770/

informed consent was obtained from the children's parents. The study was registered in the Chinese Clinical Trials Registry (ChiCTR1900027323). Between December 2019 and March 2020, 60 children undergoing cardiac surgery were enrolled in this study and were randomly divided into 2 groups, with a random number code for the sugammadex group (group S) or neostigmine group (group N), with 30 patients in each group. Among the study participants, there were 22 cases of atrial septal defect and 38 cases of ventricular septal defect. Inclusion criteria were children ages 1-to-6 of either sex, with an American Society of Anesthesiologists physical status of II to III. Exclusion criteria were patients with severe pulmonary hypertension, hepatic and renal dysfunction, severe malnutrition, duration of cardiopulmonary bypass >90 minutes, and serious perioperative complications. The investigators and surgeons were blinded to the groupings in this study.

Anesthesia Methods

All children were fasted for 6-to-8 hours before surgery and were not given any premedication. After entering the operating room, pulse oxygen saturation, electrocardiogram, heart rate (HR), and noninvasive arterial pressure were monitored using an anesthesia monitor for children, and peripheral venous access was established. Anesthesia was induced with intravenous midazolam, 0.1 mg/kg, propofol, 2 mg/kg, sufentanil, 1 μg/kg, and rocuronium (Organon, Amsterdam, Netherlands), 0.6 mg/kg. After oral intubation, the lungs were mechanically ventilated under the pressure-controlled mode. The respiratory parameters were set as follows: the tidal volume was 8 mL/kg, respiratory rate was 12-to-20 breaths/min, the ratio of inspiration to respiration was 1:1.5 to 2, and the driving pressure was adjusted to maintain an end-tidal pressure of carbon dioxide between 35 and 45 mmHg. Anesthesia was maintained with 2% to 3% sevoflurane (Jiangsu Hengrui Medicine, Lianyungang, Jiangsu, China) and intravenous sufentanil (Yichang Renfu Pharmaceutical Co, Yichang, Hubei, China), 0.5 to 1 μg/kg/h. Muscle relaxation was monitored by train-of-four (TOF) stimulation (TOF-Watch SX; Organon) on the right ulnar nerve, and rocuronium, 0.8-to-1.0 mg/kg/h, was infused continuously to maintain a TOF value <5% during surgery. An internal jugular vein catheter was inserted for infusion, and an arterial catheter was inserted for continuous hemodynamics monitoring. The cardioplegic solutions used to induce cardiac arrest were the same in both groups. During cardiopulmonary bypass, the rectal temperature was kept between 31.0°C and 34.0°C. Anesthetics were discontinued at the time of skin suture. At the end of surgery, the analgesia pump, which contained analgesic solutions of sufentanil, 1.5 μg/kg diluted in 100 mL of normal saline, was initiated (background dose of 2 mL/h, lockout time of 15 minutes, and bolus dose of 1 mL), and the study participants were transferred to the intensive care unit (ICU).

Relaxant Reversal

In the ICU, data were recorded automatically by the software TOF-Watch SX Monitor V2.2. Sugammadex, 4 mg/kg, was administrated in group S, whereas neostigmine, 30 ug/kg, and atropine, 15 ug/kg ,were administrated in group N when the TOF value was ≥0.25 or a response to TOF stimulation was present. The HR, invasive arterial blood pressure, and central venous pressures were measured continuously.

Extubation Criteria

Ventilation was supported by a ventilator in the ICU, and ventilation parameters were adjusted according to arterial blood gas analysis. Extubation criteria were as follows: (1) TOF value >0.9; (2) spontaneous breathing recovery (pulse oxygen saturation >94%, tidal volume >6 mL/kg, and partial pressure of carbon dioxide <45 mmHg); (3) arterial pH between 7.35 and 7.45; (4) no obvious active bleeding; and (5) awake.

Outcomes Measures

The following outcome measures were recorded: (1) HR and blood pressure 5 minutes after drug administration; (2) recovery time to TOF of 0.9 and extubation time; (3) drug-related side effects, such as nausea and vomiting, bradycardia, hypotension, and reintubation (bradycardia was defined as HR <80% of baseline, and hypotension was defined as mean arterial pressure [MAP] <80% of baseline); and (4) pulmonary complications (eg, atelectasis, lung infection, and hypoxemia) (atelectasis was defined as the presence of high-density images and reduction of lung volumes on chest x-ray; lung infection was defined as cough, fever with body temperature >38.5°C, and the presence of high-density images on chest x-ray; and hypoxemia was defined as an oxygen saturation <91% when inhaling air).

Statistical Analysis

The primary outcome was the extubation time. According to a previous study[11] and the authors' clinical experience, 20 patients in each group were included at an α error of 0.05 and power of 0.80. Considering possible dropouts, 10 additional participants were included in the present study, and the final sample size was 30 in each group.

SPSS software, Version 22.0 (IBM Corp, Armonk, NY), was used to perform statistical analysis. Measurement data of normal distribution were expressed as mean ± standard deviation, and the *t* test was used for analysis. The data of non-normal distribution were expressed with the quartile interval and Mann-Whitney *U* test. Numerous data were expressed with numbers, and the chi-square test was used for analysis. A $p < 0.05$ was considered to be statistically significant.

Results

Sixty children were enrolled in the present study and completed the trial (Fig 1). There were no significant differences in age, height, weight, sex, surgery type, rectal temperature,

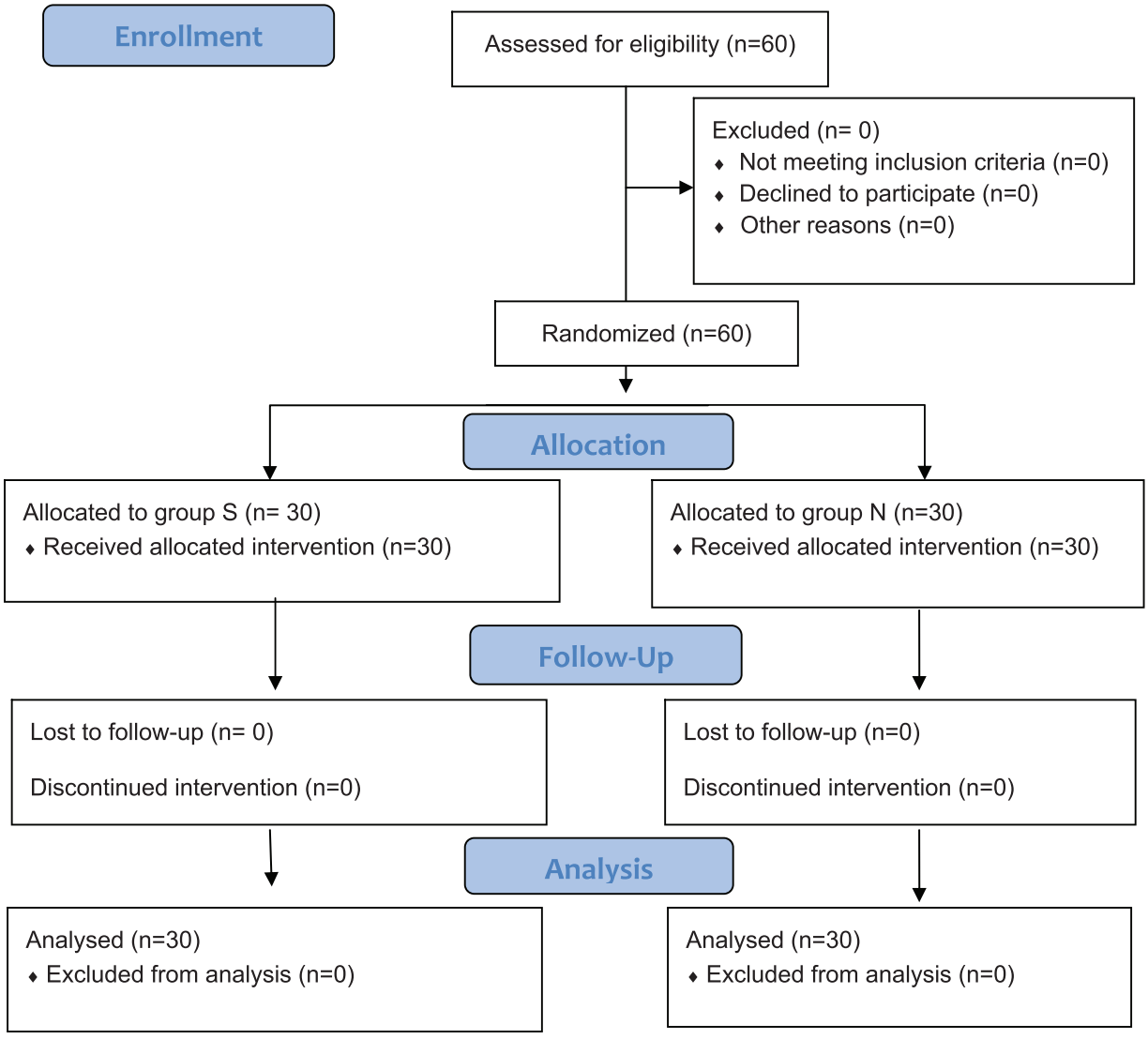

Fig 1. Flow diagram of study.

Table 1
Characteristics of Study Participants

Index	Group S (n = 30)	Group N (n = 30)	p Value
Age (y)	3.2 ± 0.8	3.1 ± 1.1	0.734
Height (cm)	103.1 ± 7.8	104.8 ± 9.2	0.438
Weight (kg)	14.2 ± 1.7	14.0 ± 1.9	0.671
Sex (male/female)	14/16	12/18	0.602
ASD/VSD (n)	9/21	13/17	0.284
Rectal temperature (˚C)	32.1 ± 0.6	32.4 ± 0.7	0.143
Duration of anesthesia (min)	131.0 ± 8.3	128.6 ± 8.2	0.281
Cardiopulmonary bypass time (min)	53.5 ± 8.4	51.6 ± 9.0	0.405

NOTE. Data are expressed as the mean (standard deviation) or number.
Abbreviations: ASD, atrial septal defect; N, neostigmine and atropine; S, sugammadex; VSD, ventricular septal defect.

duration of cardiopulmonary bypass, and duration of anesthesia between the 2 groups ($p > 0.05$) (Table 1).

The HR and MAP decreased after drug administration in both groups compared with values before drug administration ($p < 0.05$) (Fig 2). The HR after drug administration was higher in group S than in group N, whereas the MAP after drug administration was similar in both groups. There were significant differences in the HR after drug administration between the 2 groups (102.7 ± 9.4 beats/min *v* 96.9 ± 8.5 beats/min, respectively; $p = 0.03$).

The recovery time to TOF of 0.9 and extubation time are shown in Table 2. The recovery time to TOF of 0.9 and extubation time were significantly shorter in group S than in group N (3.4 ± 1.2 min *v* 76.2 ± 20.5 min and 31.0 ± 6.4 min *v* 125.2 ± 21.6 min, respectively; $p < 0.01$). The lengths of stay in the hospital and ICU were shorter in group S compared with group N (5.8 ± 1.0 d *v* 6.5 ± 0.9 d and 1.2 ± 0.2 d *v* 1.6 ± 0.4 d, respectively; $p = 0.05$). The hospitalization expenses were

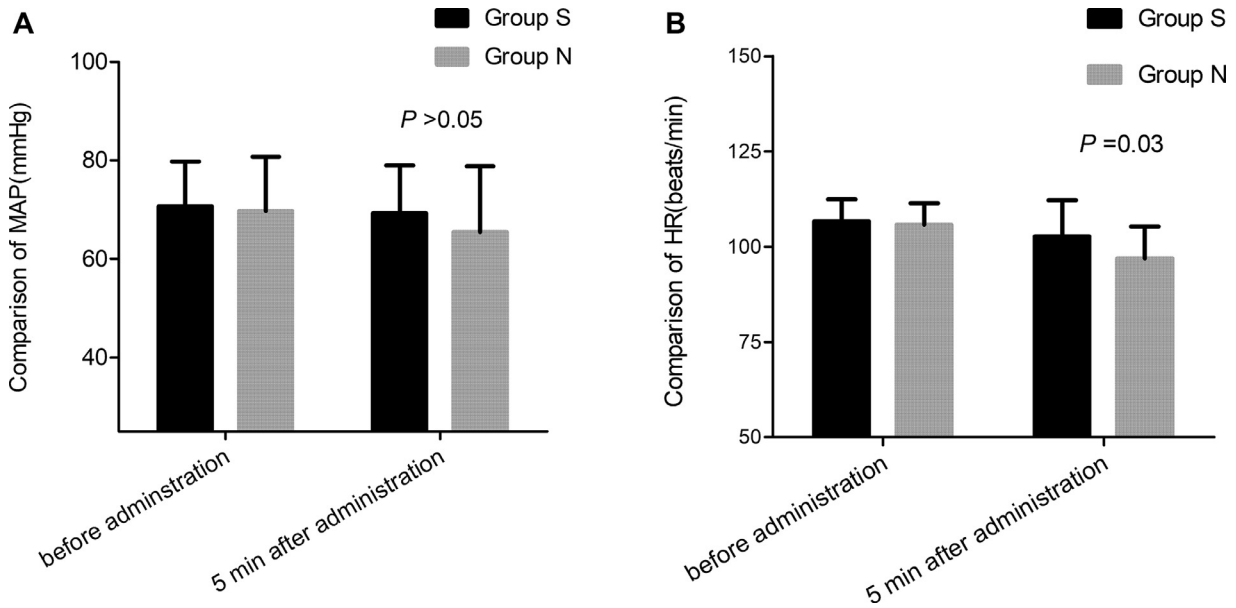

Fig 2. Hemodynamic parameters after drug administration in the 2 groups HR, heart rate; MAP, mean arterial pressure. *p < 0.05.

Table 2
Recovery Time to TOF of 0.9; Extubation, Hospital, and ICU Stay Times; and Hospitalization Expenses (n = 30)

Index	Group S	Group N	p Value
The recovery time to TOF of 0.9 (min)	3.4 ± 1.2	76.2 ± 20.5	< 0.01
Extubation time (min)	31.0 ± 6.4	125.5 ± 21.6	< 0.01
Postoperative hospital stay (day)	5.8 ± 1.0	6.5 ± 0.9	0.03
ICU stay (d)	1.2 ± 0.2	1.6 ± 0.4	< 0.01
Hospitalization expenses ($)	1,036 ± 114	1,286 ± 187	< 0.01

NOTE. Data are expressed as the mean (standard deviation). Comparison between the 2 groups, p < 0.05.
Abbreviations: ICU, intensive care unit; N, neostigmine and atropine; S, sugammadex; TOF, train of four.

Table 3
Side Effects in Both Groups (n = 30)

Index	Group S	Group N	p Value
Atelectasis (n)	0	6	0.024*
Lung infection	1	2	0.999
Hypoxemia (n)	0	1	0.999
Bradycardia (n)	0	0	0.999
Hypotension (n)	0	0	0.999
Nausea and vomiting (n)	1	3	0.612
Reintubation (n)	0	0	0.999

NOTE. Data are expressed as number. Comparison between the 2 groups.
Abbreviations: N, neostigmine and atropine; S, sugammadex.
* p < 0.05

decreased in group S compared with group N ($1,036 ± $114 *v* $1,286 ± $187; p < 0.01).

The incidences of hypoxemia, lung infection, bradycardia, hypotension, and nausea and vomiting were similar between the 2 groups (p > 0.05). Six cases of atelectasis occurred in group N, whereas no atelectasis was observed in group S; there was significant difference in the incidence of occurrence between the 2 groups (p = 0.024) (Table 3). No reintubation was observed in group S.

Discussion

In the present study, sugammadex shortened the extubation time and length of hospital stay and reduced the incidence of postoperative atelectasis with fewer adverse events in children undergoing cardiac surgery. The present study indicated that sugammadex was rapid in reversing rocuronium-induced neuromuscular block and shortened the extubation time in children undergoing cardiac surgery. Sugammadex, a new antagonist of steroidal nondepolarizing muscle relaxants, combined with rocuronium in the plasma, decreases the level of free muscle relaxants in the plasma, which allows the remaining muscle relaxants to return to the plasma.[5] An et al.[12] reported that the mean extubation time was 6.23 minutes in pediatric patients undergoing entropion surgery. In the present study, the mean recovery time to TOF of 0.9 was 3.4 minutes, and the extubation time was 31.0 minutes. The mean extubation time was prolonged significantly compared with previous studies (31.0 *v* 6.5 min). The main reasons were probably as follows: (1) the dose of analgesics—in cardiac surgery, the dose of analgesics (sufentanil) is more than that in noncardiac surgery (entropion surgery) and (2) cardiopulmonary bypass—during cardiopulmonary bypass, a lower body temperature might have an effect on the metabolism and clearance of neuromuscular blocker.[13,14] Sugammadex shortened the extubation time, it was advantageous in the recovery of spontaneous breathing, and it shortened the duration of hospital stay.

Compared with neostigmine, the hemodynamics were more stable after sugammadex administration. HR and MAP decreased after sugammadex or neostigmine administration. The decrease in HR after drug administration was greater in group N than in group S, and changes of MAP after drug administration were similar in both groups. Alsuhebani et al.[15]

reported that the incidence of bradycardia after sugammadex administration was low and did not require treatment. These results were in good agreement with the present study's findings, which indicated that sugammadex was superior to neostigmine in maintaining HR in children undergoing cardiac surgery.

In the present study, no significant differences were observed in the incidences of hypoxemia, lung infection, bradycardia, and nausea and vomiting between the 2 groups, but there was significant difference in the incidence of postoperative atelectasis. Postoperative atelectasis, which is associated with the use of a ventilator, is a common complication in patients undergoing general anesthesia. Reducing the duration of mechanical ventilation may decrease the incidence of postoperative atelectasis. Furthermore, the early recovery of spontaneous breathing reduces postoperative atelectasis.[4] Early extubation of the tracheal catheter could reduce the incidence of pulmonary complications in patients undergoing cardiac surgery.[16,17] Moreover, sugammadex did not increase the risk of reintubation. Hence, sugammadex could be used safely in fast-track cardiac surgery in pediatrics.

One limitation of the present study was its small sample size. A larger population is required to study pulmonary complications. Another limitation was that the safety of sugammadex administration in children for fast-track cardiac surgery needs further investigation.

Conclusions

Sugammadex can shorten the extubation time and reduce the incidence of postoperative atelectasis , with fewer adverse events in children undergoing cardiac surgery. It may be beneficial to use sugammadex for fast-track surgery in children undergoing cardiac surgery.

Conflicts of Interest

None.

References

1 Neirotti RA, Jones D, Hackbarth R, et al. Early extubation in congenital heart surgery. Heart Lung Circ 2002;11:157–61.

2 Akhtar MI, Momeni M, Szekely A, et al. Multicenter international survey on the clinical practice of ultra-fast-track anesthesia with on-table extubation in pediatric congenital cardiac surgery. J Cardiothorac Vasc Anesth 2019;33:406–15.

3 Wang ZC, Chen Q, Cao H, et al. Fast-track cardiac anesthesia for transthoracic device closure of perimembranous ventricular septal defects in children: A single Chinese cardiac center experience. J Cardiothorac Vasc Anesth 2019;33:1262–6.

4 Garg R, Rao S, John C, et al. Extubation in the operating room after cardiac surgery in children: A prospective observational study with multidisciplinary coordinated approach. J Cardiothorac Vasc Anesth 2014;28:479–87.

5 Akhtar MI, Hamid M, Minai F, et al. Safety profile of fast-track extubation in pediatric congenital heart disease surgery patients in a tertiary care hospital of a developing country: An observational prospective study. J Anaesthesiol Clin Pharmacol 2014;30:355–9.

6 Xu J, Zhou G, Li Y, et al. Benefits of ultra-fast-track anesthesia for children with congenital heart disease undergoing cardiac surgery. BMC Pediatr 2019;11(19):487.

7 Iezzi F, Di Summa M, Sarto PD, et al. Fast track extubation in paediatric cardiothoracic surgery in developing countries. Pan Afr Med J 2019;32:55.

8 Takazawa T, Mitsuhata H, Mertes PM. Sugammadex and rocuronium-induced anaphylaxis. J Anesth 2016;30:290–7.

9 Won YJ, Lim BG, Lee DK, et al. Sugammadex for reversal of rocuronium-induced neuromuscular blockade in pediatric patients: A systematic review and meta-analysis. Medicine (Baltimore) 2016;95:e4678.

10 M1 Carron, S Veronese, Foletto M, et al. Sugammadex allows fast-track bariatric surgery. Obes Surg 2013;23:1558–63.

11 Ammar AS, Mahmoud KM, Kasemy ZA. A comparison of sugammadex and neostigmine for reversal of rocuronium-induced neuromuscular blockade in children. Acta Anaesthesiol Scand 2017;61:374–80.

12 An J, Lee JH, Kim E, et al. Comparison of sugammadex and pyridostigmine bromide for reversal of rocuronium-induced neuromuscular blockade in short-term pediatric surgery: A prospective randomized study. Medicine (Baltimore) 2020;99:e19130.

13 Kim KM, Kwak JG, Shin BC, et al. Early experiences with ultra-fast-track extubation after surgery for congenital heart disease at a single center. Korean J Thorac Cardiovasc Surg 2018;51:247–53.

14 Waseem Z, Lindner J, Sgouropoulou S, et al. The independent risk factors for fast-track failure using a predefined fast-track protocol preselected in cardiac surgery patients. J Cardiothorac Vasc Anesth 2015;29:1461–5.

15 Alsuhebani M, Sims T, Hansen JK, et al. Heart rate changes following the administration of sugammadex in children: A prospective, observational study. J Anesth 2020;34:238–42.

16 Ji Q, Mei Y, Wang X, et al. Risk factors for pulmonary complications following cardiac surgery with cardiopulmonary bypass. Int J Med Sci 2013;10:1578–83.

17 Naveed A, Azam H, Murtaza HG, et al. Incidence and risk factors of pulmonary complications after cardiopulmonary bypass. Pak J Med Sci 2017;33:993–6.