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Effects of sugammadex on postoperative respiratory management in children with congenital heart disease: a randomized controlled study

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ABSTRACT

Background: Early extubation can reduce pulmonary complications in children undergoing cardiac surgery. The aim of this study is to evaluate the effects of sugammadex for postoperative respiratory management in children with congenital heart disease.

Methods: Sixty children with congenital heart disease undergoing elective cardiac surgery were divided into group S and group C (30 children in each group). When post tetanic twitches count (PTC) = 1-2 and train-of-four (TOF) = 0, the children in group S received sugammadex4 mg/kg for reversal of neuromuscular block at the end of surgery, and the children in group C received the same volume of normal saline. The recovery time to TOF of 0.9, the mechanical ventilation and extubation times were recorded. On the other side, the hemodynamic parameters before and 5 min after administration, and side effects were also recorded. The levels of C-reactive protein (CRP) and procalcitonin (PCT) before and 24 h after surgery were measured.

Results: The recovery time to TOF of 0.9 and extubation time were significantly shorter in the group S than in the group C (4.2 ± 1.4 vs 108.2 ± 26.7 min, 66.3 ± 6.5 vs 171.6 ± 23.1 min, respectively, $P < 0.01$). The CRP and PCT levels were found to be increased in both groups at postoperative 24 h than before surgery. Further, the levels of PCT and CRP at postoperative 24 h were lower in group S when compared to group C (median, 7 vs 17.5 mg/ml, 1.76 vs 5.22 ng/ml, respectively, $P < 0.05$). There were no statistical differences observed between the two groups ($P > 0.05$) with respect to side effects.

Conclusion: Sugammadex is rapid and effective in reversing rocuronium-induced neuromuscular block, and significantly reduces the extubation time and the release of postoperative CRP and PCT in children with congenital heart diseases.

1. Introduction

Anesthesia, cardiopulmonary bypass, and stress response can increase the incidence of postoperative pulmonary complications in patients undergoing cardiac surgery, [1–3] Mechanical ventilation is the primary risk factor for the development of ventilator-associated pneumonia; the length of mechanical ventilation plays a key role in increasing the incidence of ventilator-associated pneumonia.[4,5] Early extubation can reduce pulmonary complications in children undergoing cardiac surgery. [4] Besides, postoperative residual neuromuscular block can increase the postoperative pulmonary outcomes such as atelectasis and delayed recovery. [6,7] Anticholinesterases may lead to cardiovascular complications when used for reversal of postoperative residual neuromuscular block, and it is fatal to the patients with heart disease.[8] Sugammadex, a new antagonist for neuromuscular block, can rapidly reverse the neuromuscular block induced by steroidal nondepolarizing muscle relaxants.[9,10] Apparently, it can shorten the extubation time and reduce the postoperative hemodynamic complications in the absence of neuromuscular monitoring.[11] Thus, the present study explores the effects of sugammadex for enhanced recovery after surgery in children with congenital heart disease.

2. Materials and methods

The study was approved by the ethics committee of Shanghai children's hospital (Approval number: scmcirb-k2018086). A written

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informed consent was obtained from the guardian of the children. The study was registered in Chinese Clinical Trials Registry (Registration number: ChiCTR1900027323). From November 2019 to February 2020, a total of 60 children with congenital heart disease were enrolled in this study and divided into two groups, sugammadex group (S group) and control group (C group) with 30 cases in each group. Among them, there were 27 cases of atrial septal defect and 33 cases of ventricular septal defect. Inclusion criteria: ASA grade II-III, age from 2 to 6 years and either gender. Exclusion criteria: respiratory tract infection and other infectious diseases before operation, severe pulmonary hypertension, chronic hepatic and renal dysfunction, severe malnutrition, duration of cardiopulmonary bypass > 90 min and arterial blocking time > 50 min, and serious perioperative complications.

3. Anesthesia methods

All children were fasted for 6 hours prior to surgery. After entering operation room, pulse oxygen saturation, electrocardiogram, heart rate and non-invasive arterial pressure were monitored by anesthesia monitor for the children, and venous access was established. Anesthesia was induced with intravenous midazolam 0.1 mg/kg, propofol 2 mg/kg, sufentanil 0.5 μg/kg and rocuronium (Oganon company, Holland) 0.6 mg/kg. The children were intubated orally with the video laryngoscope, and the lungs were mechanically ventilated under the pressure-controlled mode. The respiratory parameters were set as follows: the driving pressure was 15-20 cmH_2O, the ratio of inspiration to respiration was 1:1.5, and the driving pressure was adjusted to maintain the end-tidal pressure of carbon dioxide ($P_{ET}CO_2$) between 35-45 mmHg. Anesthesia was maintained with intravenous infusion of sufentanil 1-2 $\mu g^{-1}. kg^{-1}. h^{-1}$, rocuronium 1.0 $mg^{-1}. kg^{-1}. h^{-1}$ and inhalation of 1.5-3% sevoflurane. The internal jugular vein catheter and radial artery catheter were inserted under ultrasound guidance, and the central vein and invasive artery blood pressure were monitored continuously. The cardioplegic solution was used to induce cardiac arrest: 20 ml of 5% $NaHCO_3$, 6.5 ml of 20% maninitol, 4 ml of 25% $MgSO_4$, 10 ml of 10% KCL, and 3.25 ml of 2% lidocaine were diluted in 500 ml of Ringer's solution. The rectal temperature was lowered and maintained between 32.0 ˚C and 34.0 ˚C in children undergoing atrial septal defect repair, and between 30.5 ˚C and 33.0 ˚C in children undergoing ventricular septal defect repair during cardiopulmonary bypass. Midazolam 0.1 mg/kg was injected at the end of cardiopulmonary bypass, dorasone mesylate 0.3 mg/kg was given at the time of skin suture and analgesia pump was initiated with a background dose of 2 ml/h, lockout time of 15 min and bolus dose of 1 ml (1.5 ug/kg sufentanil was diluted in 100 ml of saline). At the end of surgery, the children were transferred to the cardiac intensive care unit (CICU) with retention of tracheal catheter, and the basic vital parameters such as electrocardiogram, invasive arterial pressure, central venous pressure and pulse oxygen saturation were continuously monitored.

4. Relaxant Monitor

The acceleration muscle relaxant Monitor (Oganon Company, Tof-watch SX, Netherlands) was used to measure the neuromuscular function. All acceleromyography data were recorded automatically by the software Tof-watch SX Monitor V2.2. Muscle relaxation was monitored by the train-of-four (TOF) stimulation (stimulation duration of 0.2 ms, frequency of 2 Hz and intervals of 15 s) on the ulnar nerve in right hand and by post-tetanic twitches count (PTC). When TOF = 0 and PTC = 1-2, the children in the S group were given sugammadex4 mg/kg or 0.4 ml/kg (200 mg was diluted into 20 ml of normal saline, 10 mg/ml), while the C group were given the same volume of normal saline (0.4 ml/kg).

5. Extubation criteria

In CICU, the children were ventilated with ventilator under synchronous intermittent command ventilation (SIMV) mode, and ventilatory parameters were set according to the patient's age and weight. Initial parameters were set as follows: pressure -controlled mode, tidal volume of 6-8 ml /kg, respiratory ratio of 1:1.5 ~ 2, and FiO_2 of 0.8 (air-oxygen mixture). Oxygen concentration was gradually decreased to 35%-50% according to arterial blood gas analysis. Extubation criteria were as follows: 1. TOF value more than 0.9 and airway protective reflex recovery; 2. Hemodynamics stability; 3. spontaneous breathing recovery: respiratory frequency greater than 16 breaths/min, tidal volume > 6 ml/kg and $PaCO_2$ < 45 mmHg; 4. No obvious active bleeding and electrolyte acid-base imbalance, and urine volume > 0.5 $ml.kg^{-1}. h^{-1}$; 5. Awake.

6. Outcomes measure

1 The blood pressure, central venous pressure and heart rate before and 5 min after administration were recorded.
2 The recovery time to TOF of 0.9, mechanical ventilation time and extubation time were recorded.
3 Peripheral venous blood was drawn to measure the levels of C-reactive protein (CRP) and procalcitonin (PCT) before and 24 h after surgery by automatic biochemical analyzer.
4 The arterial blood was drawn to analyze before and 5 min after extubation of tracheal catheter, and drug related side effects were also recorded.

7. Statistical analysis

The primary outcomes were the extubation time and recovery time to TOF of 0.9. According to the previous study [12] and our pilot study, twenty samples in each group were included at an α error of 0.05, and power of 0.80. Considering possible dropouts, we had included ten extra subjects in our study and hence the final sample size was increased to thirty.

SPSS 22.0 software was used to carry out statistical analysis. Measurement data of normal distribution were expressed as mean ± standard deviation (SD), and *t* test was used for analysis. The data of non-normal distribution were expressed with quartile interval and Man-Whitney U test.Numerous data were expressed with number and $\chi 2$ test was used for analysis. A $P < 0.05$ was considered statistically significant.

8. Results

Sixty children were enrolled in the study and completed this trial (Fig. 1).There were no significant differences in age, height, weight, gender, type of operation, cardiopulmonary bypass time, arterial blocking time, rectal temperature and operation time between the two groups ($P > 0.05$), while there were significant differences observed in postoperative hospital stay ($P < 0.05$, in Table 1).

The mean arterial pressure (MAP), heart rate (HR) and central venous pressure (CVP) are shown in Fig. 2. MAP, HR and CVP before and after drug administration were comparable in both groups. There were no significant differences in MAP, HR and CVP after administration between the two groups ($P > 0.05$). MAP, HR and CVP decreased after administration in both groups compared to those before administration ($P < 0.05$).

The recovery time to TOF of 0.9, mechanical ventilation and extubation time are shown in Table 2. The recovery time to TOF of 0.9, mechanical ventilation time and extubation time were significantly shorter in the group S than in the group C (4.2 ± 1.4 vs 108.2 ± 26.7 min, 62.6 ± 5.9 vs 169.5 ± 25.4 min, 66.3 ± 6.5 vs 171.6 ± 23.1 min, respectively, $P < 0.01$).

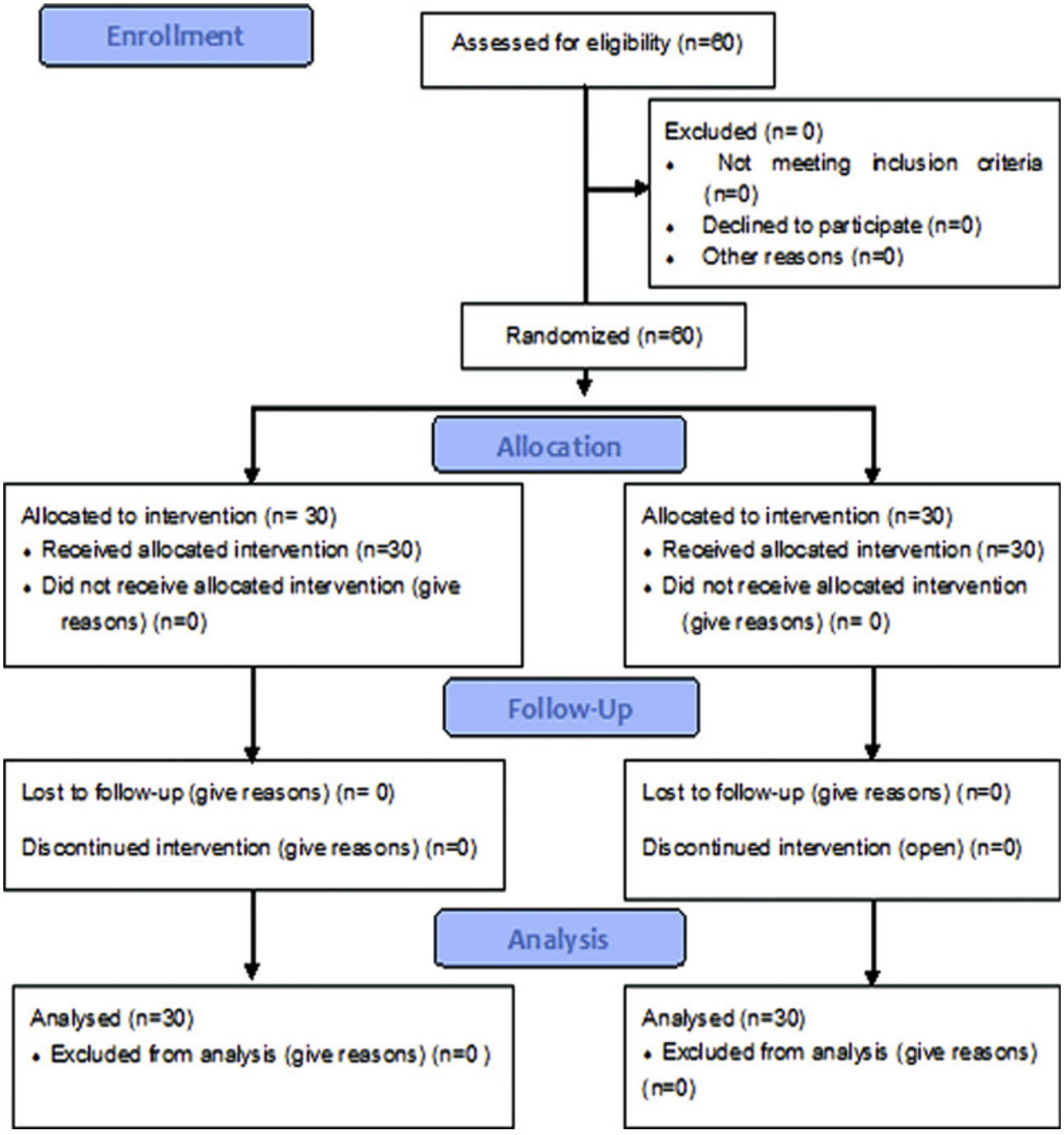

Fig. 1. Flow diagram of study.

The levels of CRP and PCT in both groups are shown in Fig. 3. At 24 h after surgery, the levels of CRP and PCT in both the groups significantly increased compared to pre-operation ($P < 0.01$), but CRP and PCT in the S group were lower than those in the C group (median, 7 vs 17.5 mg/ml, 1.76 vs 5.22 ng/ml, respectively, $P < 0.05$), and there was a statistical difference between the two groups.

The incidence of pneumonia, atelectasis, hypoxemia, re-intubation, muscular rigidity, nausea and vomiting was similar between the two groups ($P > 0.05$). Two cases of nausea and vomiting occurred in group C, while no nausea and vomiting occurred in group S. There was no significant difference in the incidence of nausea and vomiting between the two groups (Table 3) ($P = 0.49$). A case of muscular rigidity was observed in group S.

9. Discussion

Muscle relaxants facilitate the intubation of tracheal catheter and surgical procedure in pediatric cardiac surgery. However, postoperative residual neuromuscular block leads to an extension of the mechanical ventilation time, and increase in pulmonary inflammation. [13,14] In this study, we found that 4 mg/kg sugammadex could significantly shorten the mechanical ventilation time and reduce the release of CRP and PCT in children after cardiac surgery without increasing the adverse events, which might reduce the occurrence of pulmonary inflammatory response in children with congenital heart disease.

The results of current study reveal that sugammadex could rapidly reverse the neuromuscular block induced by rocuronium. Since sugammadex acts as an encapsulator of neuromuscular blocker and is

Table 1
Data of children(n = 30).

Index	Group S	Group C	P value
Age (month)	26.9 ± 9.1	27.4 ± 10.1	0.830
Height (cm)	97.0 ± 8.3	95.9 ± 9.9	0.642
Weight (kg)	12.6 ± 2.0	12.7 ± 3.3	0.591
Gender(male/female)	18/12	16/14	0.602
Type of operation(ASD/VSD)	14/16	13/17	0.795
Rectal temperature (℃)	32.8 ± 0.5	32.9 ± 0.8	0.621
Operation time (min)	117.6 ± 9.7	119.4 ± 10.8	0.484
Cardiopulmonary bypass time (min)	54.6 ± 9.4	52.8 ± 9.3	0.441
Arterial blocking time (min)	32.4 ± 7.1	32.6 ± 6.7	0.896
Postoperative hospital stay (day)	6.7 ± 0.9	7.3 ± 0.8	0.010*

Data are expressed as the mean (standard deviation) or number. Comparison between the two groups, *$P < 0.05$. ASD: atrial septal defect, VSD: ventricular septal defect.

combined with rocuronium in the plasma, it decreases the concentration of free muscle relaxants in the plasma, which allows the remaining muscle relaxants to return to the plasma, and restore muscle strength. [15] The recovery time to TOF of 0.9 and extubation time were significantly shorter in group S compared with the group C. Sugammadex can be used for achieving early extubation to reduce the mechanical ventilation time. It was beneficial for the recovery of respiratory function and reduced the duration of stay in CCU.

Ammar AS, et al. reported that sugammadex significantly shorten the pediatric extubation time (4.5 min) in non-cardiac surgery. [16] In present study, the extubation time (66.3 min) was significantly shorter in children with congenital heart disease after sugammadex

Table 2
Time to recovery of TOF, mechanical ventilation and extubation time (n = 30).

Index	Group S	Group C	*P* value
The recovery time to TOF of 0.9 (min)	4.2 ± 1.4	108.2 ± 26.7	< .0001
Mechanical ventilation time (min)	62.6 ± 5.9	169.5 ± 25.4	< .0001
Extubation time (min)	66.3 ± 6.5	171.6 ± 23.1	< .0001

Data are expressed as the mean (standard deviation). Comparison between the two groups, $P < 0.01$.

administration, but the extubation time was significantly longer than that in non-cardiac surgery (66.3 vs.4.5 min). The difference in results may be related to the operation type. Moreover, many factors affect postoperative extubation time in children undergoing cardiac surgery, such as dosage of analgesics and muscle relaxants, cardiopulmonary bypass time, arterial blocking time and body temperature. [17,18] Therefore, the extubation time was relatively longer in children undergoing cardiac surgery compared to non-cardiac surgery.

In this study, intravenous sugammadex not only significantly shortened the extubation time of tracheal catheter in children undergoing cardiac operation, but also maintained the stable hemodynamics after administration. Early extubation did not increase the risk of reintubation. Early spontaneous breathing recovery and early extubation of tracheal catheter can reduce the incidence of pulmonary complications in children with congenital heart disease. Park ES, et al. reported that sugammadex could shorten extubation time and reduce postoperative hemodynamic complications in the absence of neuromuscular monitoring in patients undergoing laryngeal microsurgery. [11] It was in good agreement with our results. It indicated that sugammadex could

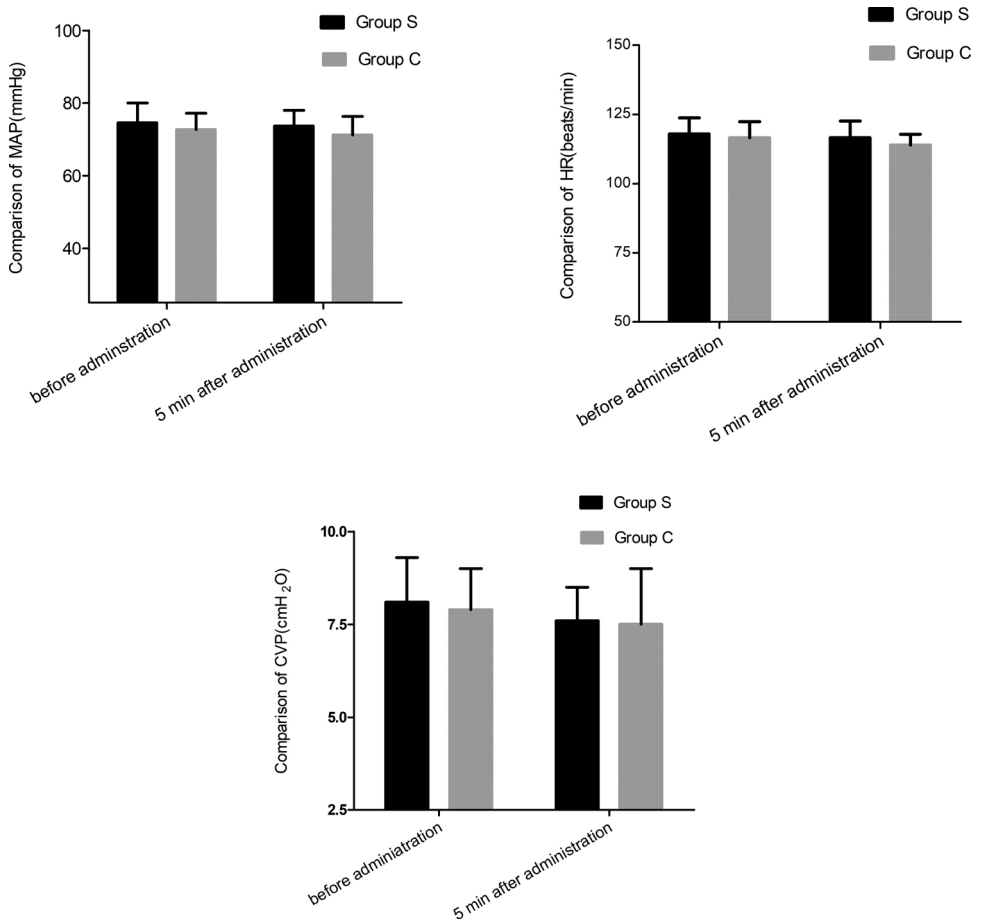

Fig. 2. Hemodynamic parameters before and after drug administration in the two groups, compared with Group C, $P > 0.05$. MAP: mean arterial pressure, HR: heart rate, CVP: central venous pressure.

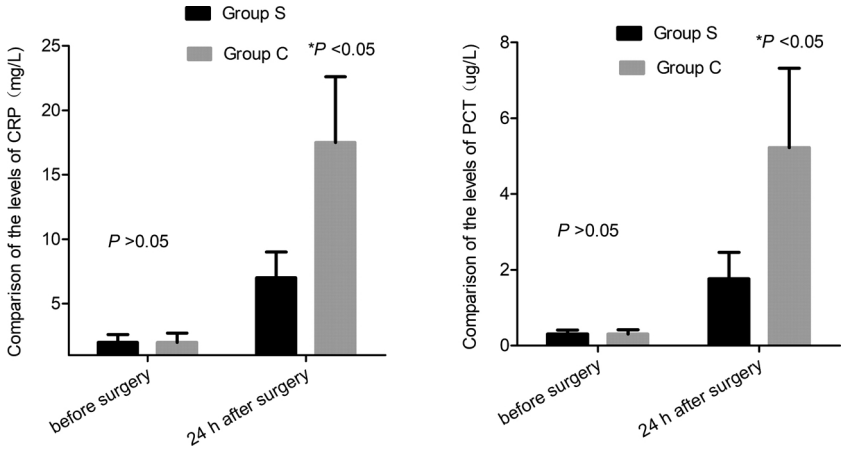

Fig. 3. Comparison of postoperative PCT and CRP content between the two groups, compared with Group C, $*P < 0.05$; compared with pre-operation, $P < 0.01$.

Table 3
Side effects in both group (n = 30)

Index	Group S	Group C	*P* value
Pneumonia (n)	0	0	0.99
Atelectasis (n)	0	0	0.99
Hypoxemia (n)	0	0	0.99
Re-intubation (n)	0	0	0.99
Nausea and vomiting (n)	0	2	0.49
Muscular rigidity (n)	1	0	0.99

Data are expressed as number. Comparison between the two groups, $P > 0.05$.

be safely used in children with congenital heart disease.

Studies reported that the incidence of ventilator-associated pneumonia was closely related to the postoperative retention time of tracheal catheter.[4,5]Shortening the time of mechanical ventilation not only alleviates the stimulation of the endotracheal tube, which lead to increases in blood pressure, heart rate and oxygen consumption, but also reduces the release of postoperative CRP and PCT, and the ventilator-associated pneumonia or lung injury.[19–21] Our study found that the levels of CRP and PCT at postoperative 24 h were significantly higher than before operation in both groups, but the levels of CRP and PCT at postoperative 24 h were lower in group S than those in group C. The previous studies reported that the PCT peaked at the first postoperative 24 h [22,23] and CRP peaked at postoperative 48 h [23], so the levels of CRP and PCT increased obviously at postoperative 24 h. The present study indicated that sugammadex could alleviate the inflammatory response as mechanical ventilation time was shorter. The length of mechanical ventilation plays a key role in increasing the incidence of ventilator-associated pneumonia. The presence of a tracheal catheter was one of the major causes for ventilator-associated pneumonia development. [24] As the levels of CRP and PCT were associated with ventilator-associated pneumonia, sugammadex might alleviate the pulmonary complication. This was in consistent with the previous study. [25]

In this study, there were no significant differences in terms of the postoperative complications between the two groups. Two cases of nausea and vomiting occurred in group C, while none was observed in group A. Similar to our findings Koyuncu O, et al. reported that sugammadex could reduce the incidence of nausea and vomiting.[26] The pneumonia, atelectasis, hypoxemia and re-intubation, were not observed in both the groups. A case of muscular rigidity was observed in group S, the reason could be due to rapid recovery from neuromuscular block. This study shows that sugammadex did not increase the incidence of adverse events.

There are some limitations in this study. Firstly, individual difference is an important consideration on the study outcome. Besides, we measured the levels of CRP and PCT only at 24 h after the operation, and continuous monitoring of CRP and PCT was not done. The dynamic change of PCT is an important factor to predict postoperative infection. [22] In our pilot study, the levels of CRP and PCT were found to be increased in both groups at postoperative 48 h than those before surgery. The levels of PCT at postoperative 48 h were lower than postoperative 24 h, and the levels of CRP at postoperative 48 h were higher than postoperative 24 h. Increase in PCT levels at postoperative 24 h was considered as early prediction of inflammation. Lastly, there was lack of long-term follow-up on respiratory complications in children.

10. Conclusions

Sugammadex can rapidly and effectively antagonize the residual neuromuscular block induced by rocuronium, shorten the postoperative extubation time and reduce the release of CRP and PCT in children undergoing cardiac surgery.

Consent for publication

Yes.

Data Availability

Authors allows researchers to verify the results of an article, replicate the analysis, and conduct secondary analyses. The data will be accessible 6 months after publication.

Authors' contributions

Study design and data analysis: J.Y and Z.W

Patient recruitment and data collection

J.Y, Z.R, X.B and W.R.

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No

Declaration of Competing Interest

None.

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