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ORIGINAL RESEARCH

Comparison of Ciprofol, Remimazolam, and Propofol on Arrhythmia Inducibility in Pediatric Supraventricular Tachycardia: A Retrospective Study

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Purpose: Propofol is a commonly used intravenous anesthetic in pediatric patients. Ciprofol and remimazolam, newly approved agents, cause minimal injection pain and demonstrate stable hemodynamic characteristics. This study aimed to evaluate their effects on arrhythmia inducibility in pediatric supraventricular tachycardia (SVT).

Patients and Methods: A retrospective analysis was conducted on the clinical data of pediatric patients with supraventricular tachycardia who underwent radiofrequency ablation under general anesthesia from May 2020 to June 2024. After excluding 28 cases, 173 patients were deemed eligible for analysis. According to the intravenous anesthesia drugs administered, the patients were classified into the propofol group (Group P), the ciprofol group (Group C), and the remimazolam group (Group R). The primary outcome measure was the arrhythmia inducibility, while the secondary outcome measures encompassed ablation success, extubation time, bispectral index (BIS) value, peri - operative relevant parameters, and the incidence of postoperative nausea and vomiting.

Results: No significant difference was observed in the arrhythmia inducibility among the three groups (97.40% vs 95.35% vs 94.34%) ($P>0.05$). The secondary outcome measures in the three groups, including ablation success ($P > 0.05$), isoprenaline use ($P > 0.05$), recurrence ($P > 0.05$) and operation time ($P > 0.05$), were similar. Additionally, there was no significant difference in the incidence rates of nausea and vomiting. Excluding the baseline BIS, the Bispectral Index values of Group R were significantly higher than those of Group P and Group C at the same time point ($P<0.05$). Moreover, the extubation time in Group R was shorter than that in Group P and Group C.

Conclusion: The effects of ciprofol and remimazolam on arrhythmia inducibility in pediatric supraventricular tachycardia were comparable to those of propofol. Both ciprofol and remimazolam are appropriate for radiofrequency ablation of supraventricular tachycardia in pediatric patients.

Keywords: arrhythmia inducibility, ciprofol, pediatric, radiofrequency ablation, remimazolam, supraventricular tachycardia

Introduction

Supraventricular tachycardia (SVT) are the most common indication for an electrophysiology study (EPS) in children, with an incidence of 20/100,000.[1,2] Atrioventricular reentry tachycardia (AVRT), atrioventricular nodal reentrant tachycardia (AVNRT) and ectopic atrial tachycardia (EAT) represent the most prevalent forms of SVT among children.[3] These three types of SVT are considered narrow complex regular tachycardias and have similar characteristics.[3] In pediatric patients with SVT, invasive EPS and radiofrequency ablation (RFCA) are typically conducted under general anesthesia. This approach aims to alleviate the pain and psychological stress endured by

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children, guarantee the absence of body movement reactions, and facilitate accurate mapping and ablation by cardiac electrophysiologist. During the EPS, the induction of SVT is essential, as reliable diagnosis and subsequent treatment cannot be effectively carried out under sinus rhythm. Nevertheless, anesthetic agents may influence the electrophysiological characteristics of the cardiac conduction system, thereby impeding the induction of SVT.[4] Previous research has indicated that under general anesthesia, AVNRT can be induced in only 74%-89% of pediatric patients.[5,6] Consequently, pediatric anesthesiologists consistently strive to select appropriate anesthetic drugs to achieve a higher induction rate during RFCA. Recent investigations have demonstrated that the success rates of SVT induction in children under inhalation and intravenous general anesthesia are comparable.[7] Some medical centers prefer to utilize intravenous general anesthesia during RFCA. Propofol, the most commonly employed intravenous anesthetic, has minimal impact on electrophysiological parameters, is conducive to the precise localization and ablation of arrhythmia lesions, and is extensively applied in RFCA.[8]

Ciprofol and remimazolam are newly introduced intravenous anesthetics that have manifested clinical advantages in various fields for both adult and pediatric patients.[9–11] Both exhibit the characteristics of rapid onset and recovery, similar to propofol. Moreover, compared with propofol, there is almost no pain during intravenous injection. The inhibitory effect on the cardiovascular system is less prominent, and hemodynamics are more stable, indicating a relatively minor influence on the cardiovascular system.[12–14] Remimazolam is metabolized by esterases in the body, independent of liver and kidney functions, and it has a specific antagonist, flumazenil, which can rapidly counteract its sedative effect. Most existing studies concentrate on the effects of ciprofol and remimazolam on cardiovascular system stability during the peri-operative period.[15–17] However, there is currently no research on the arrhythmia inducibility in pediatric SVT. In this study, we retrospectively analyzed the induction of SVT during RFCA using three intravenous anesthetics: ciprofol, and remimazolam, propofol. We hypothesized that ciprofol and remimazolam would have comparable arrhythmia inducibility to propofol, with potential advantages in the recovery profile.

Materials and Methods

Ethical Approval

This study was approved by the Hospital Ethics Committee (approval number: QFELL-YJ-2024-147) and was registered in the China Clinical Trial Registry (ChiCTR2500109472). The data were stored and managed in the electronic medical records system. As the study was retrospective, patient consent was not needed. At the same time, we anonymized the data and protected patients' privacy.

Design and Patients

The retrospective analysis was conducted on the clinical data of pediatric patients who underwent RFCA under general anesthesia for supraventricular tachycardia from May 2020 to June 2024. The inclusion criteria were as follows: American Society of Anesthesiologists (ASA) physical statusI-II; no prior history of radiofrequency ablation; SVT was diagnosed based on clinical manifestations and surface electrocardiogram (ECG) during tachycardia, and the patient required RFCA treatment due to recurrent tachycardia; anti - arrhythmic drugs were discontinued for at least 5 half - lives; total intravenous anesthesia was administered via tracheal intubation; and the same intravenous general anesthetic agent was used for both the induction and maintenance of anesthesia. The exclusion criterion was patients with incomplete perioperative clinical data.

Anesthesia Method

After the patient was admitted to the room, ECG, noninvasive blood pressure, pulse oximetry, bispectral index (BIS), and train-of-four (TOF) monitoring were routinely performed. All patients underwent total intravenous anesthesia accompanied by tracheal intubation. The choose of drugs was just driven by clinical and personal expertise. Anesthesia induction: Intravenous sufentanil (0.2~0.3 μg/kg), intravenous anesthetics and rocuronium (0.6 mg/kg) were injected intravenously. Intravenous anesthetics: propofol 2~2.5 mg/kg for Group P, ciprofol 0.6~0.8 mg/kg for Group C, and remimazolam 0.5~0.8 mg/kg for Group R. Maintenance of anesthesia: A continuous i.v. infusion of propofol at 4–8 mg/

kg/h was administered to maintain general anesthesia in group P, cipofol at 0.5–0.8 mg/kg/h in group C, and remimazolam at 0.6–1.0 mg/kg/h in group R. The patients were all given remifentanil i.v. at 3–6 μg/kg/h for anesthesia maintenance. The depth of anesthesia was mainly based on fluctuations in heart rate and blood pressure, with the assistance of BIS value monitoring. Upon completion of the procedure, the administration of all anesthetic agents was terminated, and the patient was transferred to the anesthesia recovery unit. When the TOF count equals or exceeds 3, neostigmine 0.04 mg/kg and atropine 0.02 mg/kg were injected intravenously as antagonists of muscle relaxants. After the patient regained spontaneous breathing, Group R was additionally given 0.02 mg/kg flumazenil. When the Aldrete score (mainly from the degree of Activity,respiration, Circulation,consciousness, Oxygen Saturation of the five indicators; each index is 0–2 points, with the highest score of 10 points) is greater than 9, patients can be sent back to the ward.

Surgical Approach and Postoperative Management

Electrophysiological examination was performed under general anesthesia. After percutaneous cannulation of the right internal jugular vein and the left femoral vein, a depolarization catheter was placed in the coronary sinus; one tetrode catheter was placed at the apex of the right ventricle, and the other was placed in the right high atrium. To demonstrate the accessory pathway and assess baseline conduction and refractory parameters, programmed ventricular stimulation and one additional stimulation, incremental atrial pacing first in the right ventricle and then in the right atrium, were used to identify Wenckebach's point. Arrhythmia induction was performed to differentiate the types. To this end, programmed stimulation of up to three additional stimuli was applied to the right atrium, followed by burst stimulation of different cycle lengths. If the try still failed, isoproterenol was infused at a dose of 160–300 μg/h and adjusted individually until the heart rate increased. Programmed stimulation was then continued until tachycardia was induced or a maximum of 60 min. The endpoint of ablation is within 30 minutes after ablation, and pre ablation tachycardia cannot be induced with or without isoproterenol atrial ventricular program stimulation.

Data Collection

The following information was obtained from the hospital information system: ① General information (including age, gender, and body weight), types of supraventricular tachycardia, and the presence of pre excitation. ② We collected surgical time, extubation time, and BIS values at different time points [baseline (T0), 5 minutes after intubation (T1), 5 minutes after puncture (T2), During the middle of the operation (T3), and end of operation (T4)]. ③ We collected data on perioperative parameters, including intraoperative use of isoproterenol, arrhythmia inducibility, ablation success, 6-month postoperative recurrence, and incidence of postoperative nausea and vomiting.

Statistical Analysis

SPSS (26.0) was used for the statistical processing of the data. We used the Shapiro–Wilk test to assess the normality of continuous variables. Data that conformed to a normal distribution are presented as the means ± SD. Nonnormally distributed data are presented as the median (interquartile range (IQR)) and were compared via the Mann–Whitney *U*-test. Then, we used Levene's test to assess variance homogeneity and decided to use Welch's *t* test or standard *t* test. Count data are given as the number of cases (%), and any differences are evaluated via chi-square tests or Fisher's exact tests.

Results

After excluding 28 patients from a total of 201 patients, a total of 173 children were enrolled, including 77 patients in Group P, 43 patients in Group C, and 53 patients in Group R (Figure 1). There were no significant differences in age, gender, body mass, type of supraventricular tachycardia, or preexcitation syndrome among the three groups of patients (P>0.05) (Table 1).

There was no significant difference in arrhythmia inducibility among the three groups (P>0.05) (Figure 2). The perioperative relevant parameters among the three groups were similar in terms of ablation success rate (P>0.05), the use of isoprenaline (P>0.05), the recurrence rate (P>0.05) (Table 2) and the time of operation (Figure 2). The incidence rates of nausea and vomiting were not significantly different (Table 2).

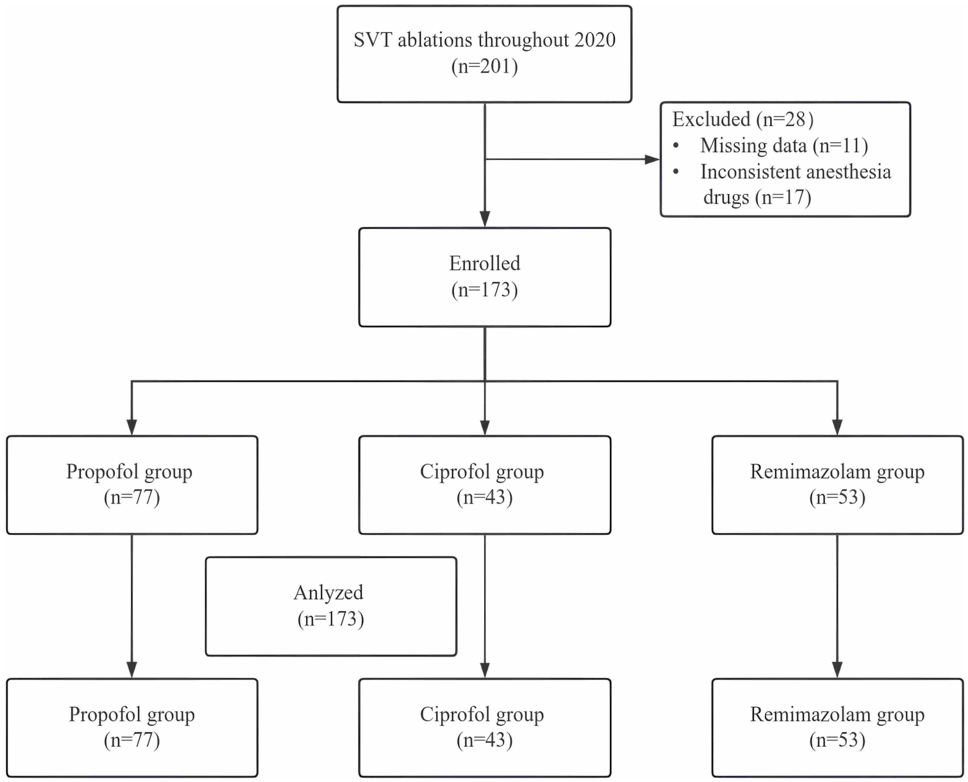

Figure 1 Flow diagram of participants.
Abbreviations:SVT, supraventricular tachycardia.

An comparison of the BIS values among the three groups revealed significant differences. Compared with Group P and Group C, Group R showed significantly greater values at the same time point (P<0.05), except for the baseline BIS (Figure 3). The comparison revealed significant differences in extubation time among the three groups, with Group R having a shorter extubation time than Group P and Group C.

Table 1 Basic Characteristics

Variables	Group P (n=77)	Group C (n=43)	Group R (n=53)	*P* value
Male	40 (51.95)	17 (39.53)	21 (39.62)	0.267
Age (years)	10.00 (6.00, 12.00)	8.00 (6.00, 11.00)	10.00 (9.00, 12.00)	0.281
Body weight (Kg)	37.90 ± 16.98	37.22 ± 14.91	42.78 ± 16.62	0.251
Type of tachycardia				0.520
AVNRT	17	10	13	
AVRT	47	29	32	
AT	13	4	8	
Preexcitation	59 (76.62)	29 (67.44)	39 (73.58)	0.551
Time of operation (min)	95.01 ± 42.46	83.95 ± 42.62	85.55 ± 34.69	0.254
Time of extubation (min)	21.60 ± 5.52	22.12 ± 5.65	17.98 ± 4.69	<0.001

Notes: The data are expressed as the means±SDs, medians (25th to 75th percentiles), or numbers of patients (percentages).
Abbreviations: AVRT, atrioventricular reentrant tachycardia; AVNRT, atrioventricular nodal reentrant tachycardia; AT, atrial tachycardia.

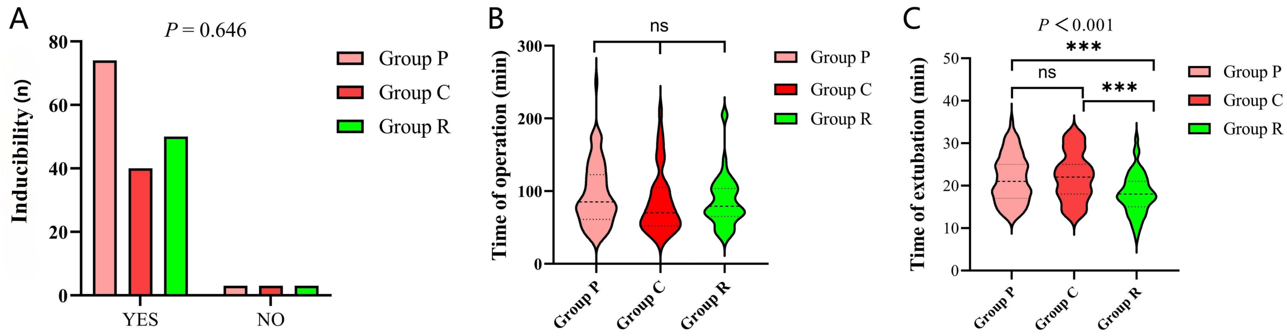

Figure 2 Comparison of ablation success rate, operation time, and extubation time among the three groups. (**A**) The success rate of ablation among three groups; (**B**) Time of operation; (**C**) Time of extubation. ***P < 0.001.

Abbreviations: Group P, propofol group; Group C, ciprofol group; Group R, remimazolam group.

Discussion

Given the distinct advantages of general anesthesia in children undergoing EPS and RFCA procedures, the 2016 expert consensus statement jointly issued by the European Pediatric and Congenital Electrophysiology Society and the Heart Rhythm Society recommended the application of general anesthesia for catheter ablation in patients aged under 12 years.[18] However, the arrhythmia inducibility is also a question worthy of study in the context of general anesthesia for children undergoing arrhythmia ablation. First, during EPS, general anesthesia may reduce the likelihood of reentrant tachyarrhythmia by reducing adrenergic tone. Second, some anesthetic drugs may also affect the electrophysiology and conduction of the heart, changing the ability to induce arrhythmias, which may negatively affect treatment.[4] Propofol is the most commonly used intravenous anesthetic drug for the induction and maintenance of general anesthesia in children. In EPS, propofol has little or no direct effect on sinus node activity or the cardiac conduction system.[19] In previous retrospective cohort studies, the SVT induction rate of propofol was between 83% and 88%.[7,20] Similar to previous studies, in this study, the induction rate of propofol group was 87.01%, and the induction rate after using isoproterenol reached 96.10%. Tachycardia induction succeeds with similar frequency under both inhalational and intravenous general anesthesia in children with AVNRT. In children with EAT, inhalational anesthesia is associated with a trend towards better inducibility. This may be related to effect of propofol in blunting the atrioventricular (AV) conduction mediated by the enhancement of the parasympathetic tone and a baroreflex inhibition.[21]

Compared with propofol, ciprofol has the advantages of mild respiratory depression, stable circulation, no injection pain, less lipid input, and greater safety.[9] In the use of ciprofol during ambulatory adenoidectomy in children, the combined application of 0.6 $mg \cdot kg^{-1}$ ciprofol and small doses of rocuronium bromide could provide satisfactory conditions for tracheal intubation, while the intraoperative circulation and BIS are stable, and the incidence of pain associated with this combination is much lower than that associated with propofol.[10] The continuous intravenous infusion

Table 2 Perioperative Relevant Parameters

Variables	Group P (n=77)	Group C (n=43)	Group R (n=53)	*P value*
Usage of isoprenaline	13 (16.88)	10 (23.26)	7 (13.46)	0.450
Arrhythmia				
Inducibility	74 (96.10)	40 (93.02)	49 (92.45)	0.646
Ablation success	75 (97.40)	41 (95.35)	50 (94.34)	0.149
Recurrence	2 (2.67)	1 (2.44)	1 (2.00)	0.582
Nausea and vomiting	6 (7.79)	4 (9.30)	4 (7.55)	0.903

Notes: The data are expressed as the means±SDs, medians (25th to 75th percentiles), or numbers of patients (percentages).

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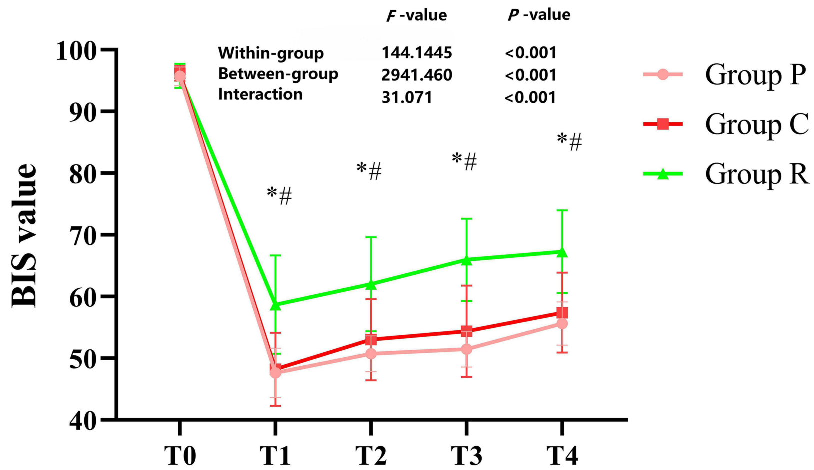

Figure 3 BIS values at different time points in the three groups. T0: baseline; T1: 5 min after intubation; T2: 5 min after puncture; T3: middle of operation. T4: the end of operation.*Indicates P < 0.001 between group P and group R at the same time point; #Indicates P < 0.001 between group C and group R at the same time point. a in each group.
Abbreviations: Group P, propofol group; Group C, ciprofol group; Group R, remimazolam; BIS, bispectral index.

of ciprofol results in less accumulation and has a greater safety factor when it is used in pediatric anesthesia.[22] There are no reports on the effects of ciprofol on the cardiac conduction system. In animal experiments, after ciprofol administration, the corrected QT interval was significantly prolonged within 1 hour of administration in a dose-dependent manner. However, the incidences of bradycardia and ECG prolongation of the QT interval are similar between ciprofol and propofol.[23] In this study, there was no significant difference in arrhythmia inducibility between ciprofol and propofol.

In EPS, midazolam is predominantly employed for sedation in adults or as an adjuvant to general anesthesia and sedation in children. At a therapeutic dosage, midazolam exerts minimal influence on the cardiac conduction system.[19] Remimazolam, a short-acting benzodiazepine, is modified by introducing a hydrolytically metabolizable methyl propionate side - chain onto the benzodiazepine ring of midazolam. The utilization of remimazolam for the induction of pediatric general anesthesia possesses the merits of propofol, namely, rapid onset of action, favorable sedation effects, stable hemodynamics, and enhanced comfort.[17] Pharmacokinetic studies have shown that remimazolam has a high clearance rate, small distribution volume, and short half-life in children. Therefore, it is a drug with good controllability for pediatric anesthesia.[24] Some case reports have shown that remimazolam has limited effects on inotropic, chronotropic, and inotropic conduction functions, making it a potentially useful drug for patients with electrophysiological problems.[25] Flumazenil, a benzodiazepine-specific antagonist, can reverse the effects of remimazolam and accelerate patient awakening.[26,27] Studies have shown that the use of flumazenil to antagonize remimazolam in pediatric patients undergoing binocular strabismus correction surgery can shorten the recovery time from anesthesia and improve the quality of awakening.[28,29] In this study, after the use of flumazenil to antagonize remimazolam in Group R, the recovery time was shortened.

Some experienced clinicians have reported that deep anesthesia can readily lead to the disappearance of arrhythmias or render them difficult to induce. Consequently, maintaining a relatively low depth of anesthesia may be a crucial factor for the induction of abnormal cardiac pacing and subsequent ablation.[30] Nevertheless, if not appropriately monitored, inadequate anesthesia may result in the patient being conscious during the operation, which could potentially cause psychological trauma and mental disorders. Alternatively, the intraoperative body movement response may inflict physical harm on pediatric patients. The BIS is one of the most commonly employed methods for monitoring the depth of anesthesia and is currently a widely recognized monitoring indicator of anesthesia depth among both adult and pediatric anesthesiologists. The literature indicates that the BIS is strongly correlated with the depth of anesthesia induced by propofol, ciprofol, and remimazolam, and it can, to a certain extent, aid in monitoring the depth of anesthesia.[31,32]

In the present study, the remimazolam group exhibited significantly higher BIS values compared to the propofo group, which is consistent with previous findings. Similar to previous studies, it was challenging to reduce the BIS value of remimazolam to less than 50. In some patients, the BIS value remained above 60 even when a large dose was administered.[32] Among 1500 patients anesthetized with remimazolam in the study by Choi et al, 61 (4.1%) met the criteria for poor maintenance of the BIS value. However, the modified Brice interview revealed that none of the patients with poorly maintained BIS values reported intraoperative awareness issues.[33] Researchers hypothesize that the possible reason for the absence of intraoperative awareness is the anterograde amnestic effect of remimazolam. Although BIS monitoring during remimazolam administration demonstrated greater variability with relatively higher values, simultaneous evaluations of neurological sedative indicators, including spectral edge frequency and resting pupil diameter, confirmed an adequate sedation level during remimazolam anesthesia.[34] According to a previous report, the resting pupil diameter, a traditional indicator of anesthesia depth, was less than 2 mm during remimazolam anesthesia. This measurement is comparable to the diameters observed during anesthesia with sevoflurane, desflurane, or propofol, despite some patients having a BIS > 60 intraoperatively with remimazolam.[34,35] Therefore, we cannot directly compare the depth of anesthesia using BIS values between anesthesia with remimazolam and propofol, and any differences in BIS may have minimal influence on the primary outcome of this study.[16] No instances of awakening, awareness, or recall were observed in the remimazolam group. However, when maintaining a low depth of anesthesia, particularly when the BIS value is above 70, attention should be paid to monitoring the patient's consciousness during surgery. However, a sustained elevation in BIS, even with the administration of appropriate dosages of anesthetic agents, can lead anesthesiologists to consider the overdose of these agents. The hemodynamic stability and resting pupil diameter during the perioperative period can assist in determining the depth of anesthesia.[16]

This limitation of the study was that it was a single-center, retrospective study. The selection and dose of anesthetic drugs were not standardized before data collection but were decided by individual anesthesia physicians on the basis of patient-specific factors and their own experience. Due to the retrospective of the study, there was no exact target range for each group to maintain BIS. In addition, the BIS value of the remimazolam group may not fully reflect the depth of anesthesia. The generalizability of the result from this study in paediatrics and different races should be tested in a large randomized prospective trial. Consequently, in the future, prospective, multicenter, and large-sample studies are required for further in-depth exploration.

Conclusions

In conclusion, the effects of ciprofol and remimazolam on arrhythmia inducibility in pediatric supraventricular tachycardia were comparable to those of propofol. Notably, the extubation time of patients in the remimazolam group was significantly shortened, which might enhance their postoperative comfort. Both ciprofol and remimazolam can be employed for radiofrequency ablation of supraventricular tachycardia in children. Moreover, large randomized controlled clinical trials can assist in elucidating the relationship between anesthetics and arrhythmia inducibility.

Abbreviations

ASA, American Society of Anaesthesiologists physical status classification; AVRT, Atrioventricular reentry tachycardia; AVNRT, atrioventricular nodal reentrant tachycardia; BIS, bispectral index; CI, confidence interval; EAT, ectopic atrial tachycardia; ECG, echocardiography; EPS, electrophysiology study; HR, heart rate; IQR, interquartile range; OR, odds ratio; RFCA, radiofrequency ablation; SVT, supraventricular tachycardia; TOF, train-of-four.

Data Sharing Statement

The data presented in this study are available from the corresponding author upon reasonable request.

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. This study was approved by the Hospital Ethics Committee (approval number: QFELL-YJ-2024-147) and was registered in the China Clinical Trial Registry (ChiCTR2500109472).

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Author Contributions

All authors contributed significantly to the work, including conception, design, execution, data acquisition, analysis, and interpretation. They participated in article drafting, revision, or review, approved the version for publication, agreed on the submitted journal, and accepted accountability for the work.

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Disclosure

The authors declare that they have no conflicts of interest.

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