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ORIGINAL RESEARCH

Ciprofol in Children Undergoing Adenoidectomy and Adenotonsillectomy: A Retrospective Cohort Study

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Objective: Ciprofol is a novel anesthetic agent, its efficacy and safety had been verified and its clinical implementation has been expanded. However, the knowledge about ciprofol in children is meager. The aim of study is to evaluate the safety and effectiveness of ciprofol in general anesthesia in children undergoing adenoidectomy and adenotonsillectomy, compared with propofol.

Materials: We retrospectively analyzed data of children who underwent adenoidectomy or adenotonsillectomy with general anesthesia from June to August 2023 to evaluate the safety and effectiveness of ciprofol. The primary outcomes included hemodynamic changes during induction and postoperative complications in post-anesthesia care unit. The secondary outcomes were extubation time, pediatric anesthesia emergence delirium (PAED) score. Meanwhile, subgroup analysis was performed based on age.

Results: 301 children met the inclusion criteria, 157 received ciprofol induction and 144 received propofol. Patient demographics and operation-related information were similar in the two groups. However, the dosage of dexmedetomidine in the propofol group was significantly higher than that of the ciprofol group (p=0.001). The trends of hemodynamic shift during induction and intubation were the same in the two groups. The PAED scores on post-extubation 10min and 20min were significantly reduced in the ciprofol group (p<0.001 and p=0.046). Moreover, in the ≤72 months and the >72 months subgroups, the scores were also significantly lower in the ciprofol group on post-extubation 10min. With the score of >10, the incidence of emergence delirium of the ciprofol group was significantly lower on post-extubation 10min and 20min in the population and the ≤72 months subgroups (p=0.03 and p=0.02). There were no obvious postoperative complications in both groups.

Conclusion: Ciprofol exhibited advantageous characteristics in the induction of children, such as stable hemodynamics, a relatively lower incidence of postoperative delirium without apparent post-anesthesia complications. Ciprofol may emerge as a novel option for general anesthesia in pediatric patients.

Keywords: ciprofol, propofol, adenoidectomy, child, general anesthesia, delirium

Introduction

Ciprofol, as a novel intravenous anesthetic agent, is a structural analogue of propofol, whose R-chiral center and cyclopropyl increase the pharmacological and physicochemical properties. The most obvious pharmacological characteristic is stronger affinity with the gamma-aminobutyric acid-A receptor.[1] These chemical structural changes give ciprofol more stable hemodynamics, with less respiratory depression than propofol in general anesthesia (GA) induction, as well as less injection pain.[2]

After the completion of Phase IV clinical trials, the pharmacokinetics, pharmacodynamics, clinical efficacy and safety of ciprofol were evaluated and summarized.[3,4] From early deep sedation in scheduled outpatients, its clinical application has been expanded to induction and maintenance in elective surgery, and to continuous sedation in the intensive care

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unit.[5–8] Not only that, ciprofol has been used in more complicated surgeries, such as cardiac surgery with cardiopulmonary bypass and kidney transplantation due to its cardiac and renal protective effects.[9–11] Besides above-mentioned clinical researches, ciprofol was also a viable option of induction in elderly patients because of its confirmed safety, in which the mean age was beyond 72 years.[12]

Given the much rarer use in pediatric patients, except for a randomized clinical study of ciprofol in children undergoing tethered cord surgery,[13] there is currently a lack of large-size studies of ciprofol in children. Thus, we conducted this real-world retrospective cohort study based on medical records of children undergoing adenoidectomy or adenotonsillectomy to confirm the safety and effectiveness in them. This was also why ciprofol was only used for induction but not for GA maintenance in children in our institution. We presumed that GA induction with ciprofol would be as safe as propofol in children.

The aims of the retrospective cohort study are to (1) determine the safety and effectiveness of induction with ciprofol in children, (2) investigate the impact of ciprofol on the short-term post-anesthesia complications. These data should be instrumental in the future use of ciprofol in children as a new intravenous anesthetic agent.

Materials and Methods

Study and Setting

This retrospective, observational, single-center study was approved by the Medical Ethics Committee of Shenzhen University General Hospital (KYLLMS-04). The written informed consent was not required because of the retrospective nature without direct impact on subjects and anonymity of the data. This registration of the study was completed before data collection at the Chinese Clinical Trial Registry (http://www.chictr.org.cn, Jun Xiong) on 27/10/2023. The registration number was ChiCTR2300077057. The study was performed according to the guidelines of Ethics Approval. All methods were conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement and the Declaration of Helsinki.

Study Design and Patient Cohort

All pediatric patients who received adenoidectomy or adenotonsillectomy under GA at this tertiary care academic teaching hospital between June and August 2023 were included in the study. The inclusion criteria were as follows: American Society of Anesthesiologists I–II, age less than 18 years. The exclusion criteria were as follows: children with preoperative respiratory infection, intraoperative incidents (massive hemorrhage), and urgent complications in post-anesthesia care unit (PACU), bleeding in the operative site and unplanned re-operation, mental diseases and/or epilepsy medical history, insufficient data.

Based on the different intravenous anesthetic agents of induction, all subjects were then divided into two groups that were ciprofol exposure group (C group) and propofol exposure group (P group). The process of patient selection is shown in Figure 1.

In our institution, the operation of adenoidectomy or adenotonsillectomy in children was not only with very short operative duration, but also with a large amount of these cases. Therefore, the protocol of induction includes 0.2mg/kg mivacurium chloride, 2μg/kg remifentanil, 2~3mg/kg propofol, and 0.1~0.3μg/kg dexmedetomidine. Meanwhile, 3~4% sevoflurane and 0.1~0.15μg/kg/min remifentanil were used in anesthesia maintenance with the bispectral index target range of 40~60. Because the clinical application of ciprofol was authorized at the beginning of this year, and less injection pain, thus some anesthesiologists used 0.5~0.6mg/kg ciprofol instead for propofol in children. Besides this, other anesthesia protocol of adenoidectomy and adenotonsillectomy did not change. At the end of operation, sevoflurane and remifentanil were discontinued, and all children were sent to PACU for postoperative extubation and recovery, except the last one in each operating room.

Data and Outcomes

Data were collected retrospectively from DHC system (DHC Software Co., Ltd, Beijing, China) and Operation-Anesthesia Management System (Chengdu Senton Netease Medical Science & Technology Development CO., Ltd, Chengdu, Sichuan, China). Patients were tracked between databases with a unique in-patient identifier.

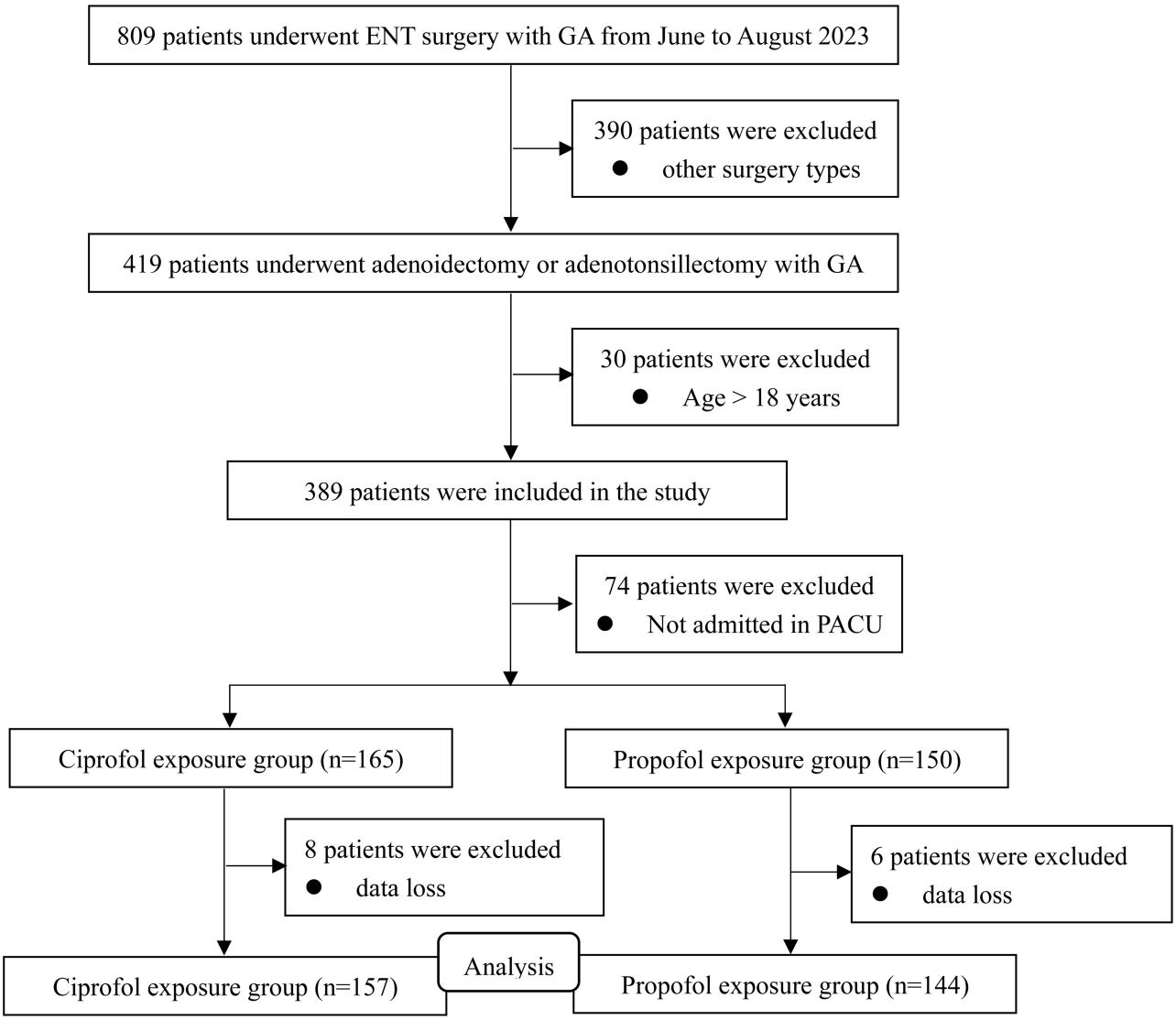

Figure 1 Flow diagram showing the process used to select patients for inclusion in this retrospective cohort study. ENT: Ear-nose-throat; GA: General anesthesia; PACU: Post anesthesia care unit.

The preoperative demographic characteristics collected at baseline included age, gender, height, weight, body mass index (BMI). Intraoperative variables included hemodynamics, volume of fluid infusion and blood loss, operation duration, and administered medicines. PACU data comprised the time of spontaneous breath recovery, the time of extubation, pediatric anesthesia emergence delirium (PAED) scores, revised face-legs-activity-cry-consolability (rFLACC) scores, and incidence of complications, for example, postoperative nausea and vomiting, oxygen desaturation, laryngospasm, and cardiac arrhythmias. PAED and rFLACC scores demonstrate the degree of emergence delirium and pain, greater scores indicate greater severity.

The primary outcomes were hemodynamic changes during induction and postoperative complications. The secondary outcomes consisted of the extubation time, the time of spontaneous breath recovery, PAED scores.

Statistics Analysis

Descriptive statistical methods were used to analyze continuous and categorical variables. Continuous numerical variables were expressed as mean ± standard deviation (SD) or median [interquartile range (IQR)] based on their normality assessed with Shapiro–Wilk test and graphical representation. Categorical variables were presented as

numbers (proportions). Homogeneity of variance was evaluated by Levene's test, and the means of continuous data were analyzed via independent *t*-test or Mann–Whitney *U*-test, as appropriate. Qualitative variables were compared with Fisher's exact test. As to the hemodynamic change, their differences were measured with the method of Repeated Measures Anova. Subgroup analysis was adjusted via age (≤72 months, >72 months) to further analyze the effect of ciprofol in different subgroups of the subjects. Two-tailed with *P* value less than 0.05 was considered statistically significant. All statistics tests were performed with IBM SPSS Statistics package V26.0 (Armonk, NK, USA).

Results

General Data

A total of 301 pediatric patients were enrolled in the study. The P group and the C group were performed in 144 and 157 cases, respectively. The demographic characteristics, intraoperative variables and PACU variables between them are displayed in Table 1. The minimum age was 22 months in the P group and 27 months in the C group. The operation duration of the C group was 2min longer than that of the P group (p=0.036), therefore, the volume of fluid infusion in the C group was more than the P group (p=0.001). However, the dosage of dexmedetomidine in the C group was 1μg less than the P group (p=0.001). Except these, there was no significant difference of other variables between them.

In the ≤72 months subgroup, the differences of demographic characteristics, intraoperative and PACU variables were the same as the population mainly. However, the age of the P group was significantly younger than that of the C group (p=0.024). And the dosage of mivacurium chloride in the C group was 1mg more than the P group (p=0.013) (Table 2).

In the >72 months subgroup, the differences of the fluid infusion volume and dexmedetomidine dosage in the two groups were significant. These differences were also found in the population and the ≤72 months subgroup (Table 3).

The postoperative extubation time and the time of spontaneous breath recovery were similar in the two groups.

Table 1 Demographic Characteristics, Intraoperative and PACU Variables of Children who Underwent Adenoidectomy or Adenotonsillectomy Between June and August 2023

Characteristics	P (n=144)	C (n=157)	*p*
Age (month)	84 (52.8)	79 (48.0)	0.368
Age group			
≤72 months	49 (34.0%)	69 (43.9%)	
>72 months	95 (66.0%)	88 (56.1%)	
Gender			
Male	100 (69.4%)	94 (59.9%)	
Female	44 (30.6%)	63 (40.1%)	
Height (cm)	124 (29.9)	121 (25.5)	0.228
Weight (kg)	22 (15.5)	22 (13.0)	0.278
BMI (kg/m^2)	15.1 (3.1)	15.1 (3.2)	0.794
Intraoperative variables			
Operative duration (min)	6 (6.0)	8 (5.0)	0.036
Blood loss (mL)	1 (0)	1 (0)	0.305
Fluid infusion (mL)	100 (50.0)	150 (138.5)	0.001
Mivacurium chloride (mg)	5 (3.0)	5 (1.0)	0.763
Induction Remifentanil (μg)	45 (30.0)	45 (25.0)	0.249
Dexmedetomidine (μg)	5 (3.0)	4 (4.0)	0.001
Dexamethasone (mg)	3 (3.0)	3 (3.0)	0.906
Flurbiprofen axetil (mg)	25 (15.0)	20 (10.0)	0.053
PACU variables			
Spontaneous breath recovery time (min)	12 (9.0)	12 (9.5)	0.768
Extubation time (min)	21 (11.0)	20 (9)	0.379

Table 2 Demographic Characteristics, Intraoperative and PACU Variables of Children in Subgroup (≤72 Months)

Characteristics	P (n=49)	C (n=69)	*p*
Age (month)	50.3±9.6	54.8±11.1	0.024
Gender			
Male	35 (71.4%)	43 (62.3%)	
Female	14 (28.6%)	26 (37.7%)	
Height (cm)	106.4±6.7	107.4±8.7	0.491
Weight (kg)	16.5 (3.0)	16.5 (4.0)	0.601
BMI (kg/m^2)	14.6 (1.25)	14.8 (2.5)	0.861
Intraoperative variables			
Operative duration (min)	5 (8.0)	10 (7.0)	0.046
Blood loss (mL)	1 (0)	1 (0)	0.086
Fluid infusion (mL)	100 (100.0)	150 (110.0)	0.001
Mivacurium chloride (mg)	4 (1.0)	5 (1.0)	0.013
Induction Remifentanil (μg)	35 (10.0)	30 (10.0)	0.811
Dexmedetomidine (μg)	4 (1.0)	2 (2.0)	0.001
Dexamethasone (mg)	2 (1.0)	2 (1.0)	0.708
Flurbiprofen axetil (mg)	20 (0)	20 (0)	0.722
PACU variables			
Spontaneous breath recovery time (min)	9 (6.0)	8 (7.5)	0.807
Extubation time (min)	18.4±7.3	17.4±7.0	0.464

Table 3 Demographic Characteristics, Intraoperative and PACU Variables of Children in Subgroup (>72 Months)

Characteristics	P (n=95)	C (n=88)	*p*
Age (month)	98 (46.0)	101 (34.8)	0.958
Gender			
Male	65 (68.4%)	51 (58.0%)	
Female	30 (31.6%)	37 (42.0%)	
Height (cm)	132 (23.0)	132 (25.8)	0.637
Weight (kg)	27 (16.0)	27.3 (17.0)	0.968
BMI (kg/m^2)	15.9 (4.0)	15.5 (4.1)	0.988
Intraoperative variables			
Operative duration (min)	6 (6.0)	7 (5.8)	0.366
Blood loss (mL)	1 (0)	1 (0)	0.918
Fluid infusion (mL)	100 (50.0)	150 (150.0)	0.001
Mivacurium chloride (mg)	6 (3.0)	6 (3.0)	0.418
Induction Remifentanil (μg)	55 (35.0)	57.5 (35.0)	0.909
Dexmedetomidine (μg)	6 (4.0)	4 (5.0)	0.012
Dexamethasone (mg)	4 (2.0)	5 (2.0)	0.318
Flurbiprofen axetil (mg)	30 (20)	30 (20)	0.276
PACU variables			
Spontaneous breath recovery time (min)	14 (10.0)	14 (10.0)	0.690
Extubation time (min)	21 (12.0)	21 (10.0)	0.855

The Hemodynamic Changes of Induction in Two Groups

The hemodynamic changes during induction are demonstrated in Figure 2A, in which systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were included. These variables on baseline were similar in the two groups. Although SBP and DBP in the P group were significantly lower than those in the C group (p=0.037 and p=0.012, respectively), their actual numerical values were very close clinically.

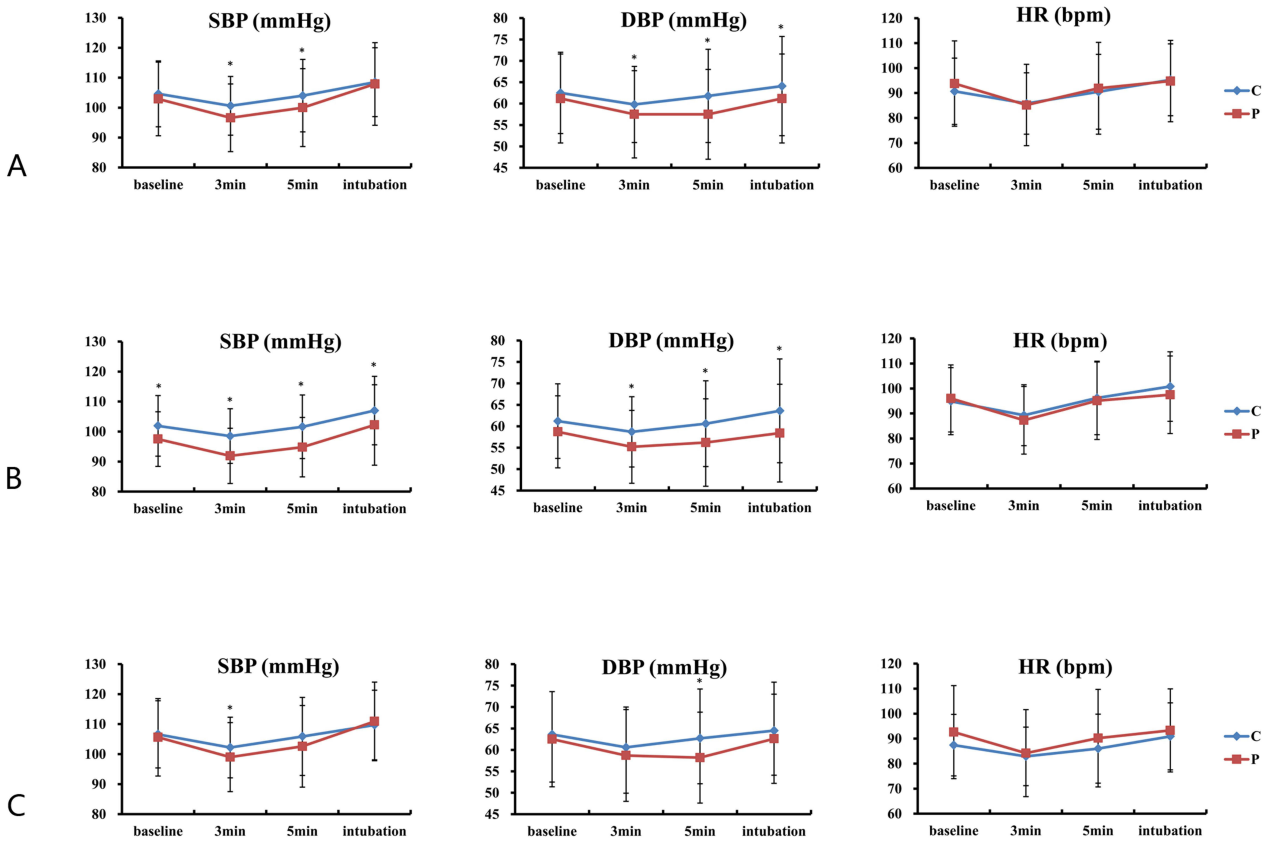

Figure 2 The hemodynamic variables in the two groups. (**A**) the total; (**B**) the subgroup of age ≤72 months; (**C**) the subgroup of age >72 months. *Compared with the C group. SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; bpm: beat per minute.

The hemodynamic changes in two subgroups (≤72 months and >72 months) are shown in Figure 2B and C.

In the ≤72 months subgroup, the SBP of baseline in the P group was significantly lower than that of the C group (p=0.017), the mean SBP were 97.5mmHg and 101.9mmHg, respectively. DBP and HR of baseline in the two groups were not different. SBP and DBP in the C group were significantly higher than those in the P group, but the differences of detailed values on every time point were very similar (Figure 2B).

In the >72 months subgroup, HR of baseline in the P group was significantly higher than that of the C group (p=0.026), the mean HR were 92.6bpm and 87.4bpm, respectively. Except this, other hemodynamic variables on every time point were similar between the two groups (Figure 2C).

From the beginning of induction to tracheal intubation, the trend of hemodynamic shift in the two groups was similar, even if in the subgroups. On 3min of post-induction, these variables were reduced significantly, followed by rising-up close to the level of baseline values after that (Figure 2A–2C).

All records of pulse oxygen saturation in the two groups on every time point were more than 99%.

PAED Score, rFLACC Score and Complications of the Two Groups in PACU

PAED scores were evaluated on post-extubation 10min, 20min, 30min and leaving PACU (Figure 3). On post-extubation 10min and 20min, PAED scores were reduced significantly by ciprofol (χ^2=13.626, p<0.001 and χ^2=9.239, p=0.046, respectively) (Figure 3A). In the ≤72 months subgroup, the differences of PAED score in the two groups were the same as the population (Figure 3B). However, in the >72 months subgroup, only the difference of PAED scores on post-extubation 10min was significant (Figure 3C).

On leaving PACU, rFLACC scores in the two groups were similar in the population and the two subgroups (Figure 3D).

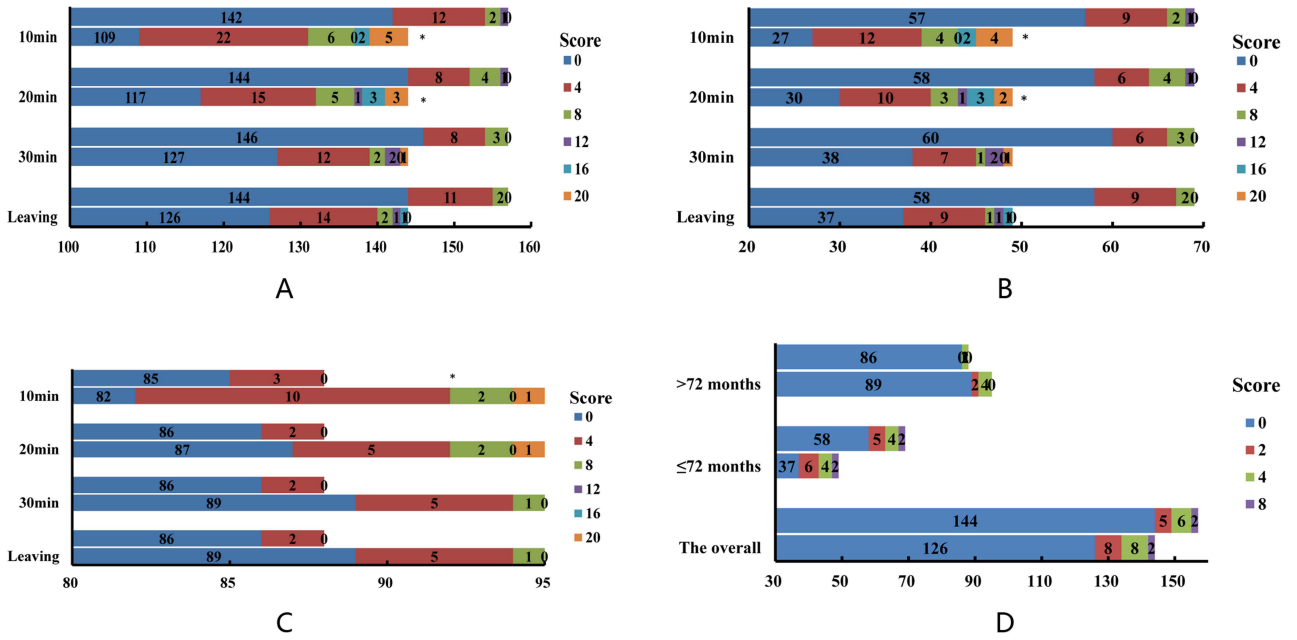

Figure 3 The cases of PAED score on post-extubation 10min, 20min, 30min and leaving PACU in the two groups. (**A**) the total; (**B**) the subgroup of age ≤72 months; (**C**) the subgroup of age >72 months; (**D**) the cases of rFLACC score in the two groups. On every time point in A, B, C subfigures and each subgroup in D subfigure, the first bar stands for the C group, the second bar is the P group. * Compared with the C group.

Table 4 The Incidence of PAED with Standard of PAED Score >10 Between the Two Groups and Subgroups on

	Post-extubation	10min	20min	30min	Leaving PACU
The population	P (n=144)	7 (4.9%)	7 (4.9%)	3 (2.1%)	2 (1.4%)
	C (n-157)	1 (0.64%)*	1 (0.64%)*	0	0
≤72 months	P (n=49)	6 (12.2%)	6 (12.2%)	3 (6.1%)	2 (4.1%)
	C (n=69)	1 (1.4%)*	1 (1.4%)*	0	0
>72 months	P (n=95)	1 (1.1%)	1 (1.1%)	0	0
	C (n=88)	0	0	0	0

Note: *Compared with the P group.
Abbreviation: PACU, post-anesthesia care unit.

If PAED score of >10 is considered as emergence delirium, on post-extubation 10min and 20min, the incidences of PAED were significantly lower in the C group both in the population (χ^2=5.180, p=0.030) and in the ≤72 months subgroup (χ^2=5.984, p=0.020) (Table 4).

In PACU, there was no incidents after extubation, for example postoperative nausea and vomiting, laryngospasm and cardiac arrhythmias. And oxygen desaturation did not take place.

Discussion

The present retrospective study demonstrated that the hemodynamic tendency during induction caused by ciprofol and propofol was similar; furthermore, more stable tendency was observed with ciprofol. There was less PAED on the early stage of post-extubation with ciprofol. Meanwhile, no obvious post-anesthesia complications appeared in PACU with ciprofol or propofol.

Ciprofol, a new anesthetic compound, has expanded from painless endoscopic examination to induction and GA maintenance, even continuous sedation for critical cases.[14] Its safety and efficacy in adults were confirmed by previous clinical trials. Although Ding and colleagues demonstrated ciprofol was safe and effective for induction in elderly patients undergoing major noncardiac surgery,[15] the study of ciprofol in children has been deficient. A prospective

randomized clinical study by Zhu explored GA with ciprofol in children, including induction and maintenance, which confirmed total intravenous anesthesia with ciprofol was safe and effective in children.[13]

Given the experience of ciprofol in children is meager, it was only authorized to use in induction in our institution. By this retrospective study, ciprofol was as effective as propofol during induction, whose results were consistent with the prospective study of Zhu.[13] During induction, partly hemodynamic variables were significantly different compared with propofol, nevertheless their clinical values were very close, and there was no obviousdifference in the subgroups. The tendency of hemodynamic changes with ciprofol and propofol was also consistent with the previous clinical trial related to ciprofol in adult induction. In the early stage of induction, SBP, DBP and HR decreased, but then returned and became stable.[16] SBP and DBP were slightly higher with ciprofol than propofol during the process of induction, which was different from adult induction.[16] We inferred the different population of patients, children and adults, might cause the difference, but this would need more studies to investigate.

Ciprofol is very suitable for children since there is less injection pain. Besides, it was as safe to administer as in adult induction without significant post-anesthesia complications, such as postoperative nausea and vomiting, laryngospasm, and cardiac arrhythmias.[13] Actually, ciprofol is safe clinically even with unexpected overdose.[17] Not only that, ciprofol did not delay spontaneous respiration recovery and extubation postoperatively, the result was consistent with the study of Zhu.[13] Additionally, prolongation of QT interval as an adverse drug reaction of ciprofol occurred in animal tests and clinical trial,[18,19] nevertheless it did not appear in this retrospective study. The study demonstrated the minimum age of ciprofol induction was 27-month-old, and the median of age was the same as that in the study of Zhu.[13] There were four children in the C group who were younger than 3 years old, but there was no postoperative complications in these children. In another study of adenotonsillectomy with ciprofol,[20] the minimum age and the ciprofol dosage were similar to our study. These familiar safety profiles in the younger children probably account for it being chosen in the very young. Till now, given only the two published studies related to ciprofol in children, more studies should be done to confirm its safety in them, even with ages younger than 3 years.

The retrospective study showed that PAED scores on early stage of post-extubation were significantly lower with ciprofol induction, whether in the population or in the subgroups. To the best of our knowledge, there was no study involving the influence of ciprofol on PAED in children. It is well known, postoperative delirium, commonly in children undergoing adenotonsillectomy, could cause postoperative bleeding, accidental removing of intravenous cannulation, other injuries, and self-extubation. Meanwhile, it increases the nursing requirements in PACU.[21] If ciprofol could reduce PAED in children, it is more suitable for children's anesthesia because of another characteristic of slighter injection pain.

According to the standard of PAED score more than 10 is the presence of postoperative delirium,[22] the ratio of PAED in the study was about 0.64% and 4.9% in the two groups respectively, and it was higher in the subgroup of age less than 6 years. These results were consisted with the previous report, in which preschool age is considered as a possible risk factor of PAED.[23] However, it is very difficult to differentiate PAED and postoperative pain in children, especially during the first minutes after awakening without complete awakening.[24] To reduce pain and the incidence of PAED, flurbiprofen axetil and dexmedetomidine were administered at the stage of induction in our institution routinely.[25,26] The amount of flurbiprofen axetil was similar in the two groups. However, the dosage of dexmedetomidine in the propofol induction group was 1μg more than the ciprofol group. In the subgroups, the difference of dexmedetomidine median unexpectedly reached to 2μg. However, the score and incidence of PAED with ciprofol induction was lower than propofol induction, though the latter was with a higher dosage of dexmedetomidine.

Dexmedetomidine has been popularly used to prevent or ameliorate PAED in children.[27,28] The effect of dexmedetomidine difference seemed unusual to be just 1μg yet significant statistically. It would be unusual to be clinically different at what amounts to a tiny dose. However, this confusion did not interfere with explaining the result of PAED score. Even if the dosages of dexmedetomidine were the same in the two groups, ciprofol not only reduced PAED scores but also ameliorated the incidence of PAED on the early post-extubation stage. Consequently, we speculated that ciprofol might reduce PAED on the early stage of post-extubation. Of course, our study was just retrospective, further verification of the effects of dexmedetomidine and ciprofol on postoperative delirium are needed with higher quality and larger scale randomized controlled trials.

Limitations

There were several limitations in this study that should be considered when interpreting our findings. First, as a retrospective study collecting electronic records, it is impossible to avoid selection bias or confounders. Second, the samples were from a single-center, and the type of surgery was very simple and short, thus the findings have not enough power to be generalized. Further studies with multi-centers and large-scale data are needed to evaluate ciprofol in much large pediatric populations. Third, because the duration of surgery is very short, the intraoperative maintenance amount of sevoflurane and remifentanil were not included, which might influence the results. Finally, this is a common problem with new drugs introduced without pediatric description, so we need to learn more about their pharmacokinetics and pharmacodynamics, for example, the concentration-response relationship for effect and adverse effects, the change with age, and drug-interactions. These could not be researched in this retrospective study, but in our ongoing randomized control clinical trial.

Conclusion

In the retrospective study, no matter ciprofol or propofol, both of them could be used in children's induction safely and effectively. Compared with propofol, the hemodynamic of ciprofol was more stable. Ciprofol did not delay postoperative extubation and produce obvious post-anesthesia complications, but also incidence of PAED was much lower on the early stage of post-extubation. However, as a novel agent, the safety and efficacy of ciprofol in children should be confirmed further with large-scale prospective randomized controlled studies in the future.

Abbreviation

DBP, Diastolic blood pressure; GA, General anesthesia; HR, Heart rate; PAED, Pediatric anesthesia emergence delirium; PACU, Post-anesthesia care unit; Rflacc, Revised Face-leg-activity-cry-consolability; SBP, Systolic blood pressure.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author by the Email address xiongjun107@hotmail.com.

Clinical Trial Registration

This trail was registered at Chinese Clinical Trial Registry (http://www.chictr.org.cn, Jun Xiong) on 27/10/2023, registration number was ChiCTR2300077057.

Ethics Approval

This trial was approved by the Medical Ethics Committee of Shenzhen University General Hospital, KYLLMS-04.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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