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Effects of propofol combined with remifentanil on hemodynamics and stress response in children undergoing surgery for oral cancers, tonsil and adenoid surgery

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The anesthetic medication to sedate a child during general anesthesia (GA) for oral cancer, adenoidectomy or tonsillectomy is associated with operative complications such as hemodynamic instability and long postoperative recovery period. The current advancement enables combination of different anesthetic medications to decrease operative or postoperative complications associated with GA. In this study assessed the effects of propofol combined with remifentanil on hemodynamics and stress response in children undergoing oral cancer, tonsil and adenoid surgery. Propofol combined with remifentanil is beneficial to anesthesia for children undergoing oral cancer tonsil and adenoid surgery, manifested as stable hemodynamics, rapid recovery, low inflammatory and stress responses, and mild adverse reactions. A total of 106 eligible children treated from May 2017 to December 2019 were randomly divided into observation and control groups (n=53). Observation group was anesthetized by propofol plus remifentanil, while control group was anesthetized by propofol plus esketamine. Mean arterial pressure (MAP), heart rate (HR), serum C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), epinephrine (E), cortisol (Cor), CD^{3+}, CD^{4+} helper and CD^{8+} inhibitory T lymphocytes, and CD^{4+}/CD^{8+}were compared before anesthesia induction (T1), immediately after intubation (T2), at the beginning of operation (T3), at the end of operation (T4) and 5 min after extubation (T5). Time of anesthetic recovery and adverse reactions after extubation were observed. MAP and HR significantly rose at T2 compared with those at T1. After maintenance of anesthesia, MAP and HR were significantly lower in observation group than those in control group. Serum CRP, IL-6 and TNF-α levels rose with time. E and Cor levels rose from T1 to T4 and declined at T5, with significant differences at each time point. CRP, IL-6, TNF-α, E and Cor levels were lower in observation group from T3 to T5. At T4 and T5, CD^{3+}, CD^{4+}levels and CD^{4+}/CD^{8+} declined, whileCD^{8+}level rose compared with those at other three time points. Time of recovery of autonomous respiration and limbs and duration from anesthetic withdrawal to extubation were significantly shorter in observation group. Observation group had lower incidence rate of dysphoria during recovery.

Keywords: Adenoidectomy, Esketamine, Tonsillectomy

Chronic tonsillitis, adenoid hypertrophy and oral cancer both malignant and benign like SCC (squamous cell carcinoma) are the main causes of upper respiratory infection and snoring in children. In severe cases, they may affect the normal development of adjacent organs, leading to distraction, memory deterioration and even mental retardation in children[1]. At present, surgical resection is the main treatment method for oral cancer, tonsils and adenoids[2]. However, due to the abundant innervations in the mouth and throat, a strong stress response, hemodynamic fluctuations and even severe complications will still be caused despite short time of operation. In clinic, general anesthesia and tracheal intubation are often adopted for analgesia and sedation. Moreover, it is required to recover completely and quickly without dysphoria after operation. Hence, choosing appropriate anesthetic drug is extremely important[3,4].

In recent years, propofol and remifentanil is used clinically for anesthesia in pediatric oral cancer resection, tonsillectomy and adenoidectomy. However, the effects of such an anesthesia method on the hemodynamics and stress response in children are rarely reported. In the present study, therefore, propofol combined with remifentanil and propofol

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combined with esketamine were compared in low temperature plasma ablation of oral cancer, tonsils and adenoids in children, aiming to explore the effects on hemodynamics and stress response, and provide a reliable clinical basis for the selection of anesthesia method.

Material and Methods

Subjects

A total of 106 children scheduled to undergo low temperature plasma ablation of oral cancer, tonsils and adenoids in our hospital from May 2017 to December 2019 were selected and randomly divided into observation group (n=53) and control group (n=53). In observation group, there were 27 males and 26 females aged 3-9 years, with an average of (5.83±1.42) years. The body weight was 14-28 kg, with an average of (21.67±6.29) kg, and the body height was 87-120 cm, with an average of (102.51±13.69) cm. In terms of the American Society of Anesthesiologists (ASA) grade, there were 30 cases in grade I and 23 cases in grade II. In terms of the Mallampati class, there were 35 cases in class I and 18 cases in class II. In control group, there were 29 males and 24 females aged 3-10 years, with an average of (5.87±1.50) years. The body weight was 15-29 kg, with an average of (22.39±6.34) kg, and the body height was 88-122 cm, with an average of (104.07±13.82) cm. In terms of the ASA grade, there were 32 cases in grade I and 21 cases in grade II. In terms of the Mallampati class, there were 34 cases in class I and 19 cases in class II. Inclusion criteria: (i) Children with resectable grade of oral cancer as per TNM staging; (ii) Children aged above 2 years, (iii) those who often suffered from recurrent colds, nasal congestion and discharge, accompanied by varying degrees of snoring and mouth breathing; (iv) those with tonsillar hypertrophy ≥degree II complicated with adenoid hypertrophy shown in clinical examination, and meeting the indications for surgical resection of tonsils and adenoids; (v) those in ASA grade I or II and Mallampati class I or II; and (vi) those whose families were informed and signed the informed consent. Exclusion criteria: (i) children with arrhythmia, congenital heart disease or other organ dysfunctions; (ii) those with obesity (20% above the standard body weight); (iii) those with mental retardation, neurological disorder or severe developmental disorder, (iv) those with airway anomaly or recent upper respiratory infection; (v) those allergic to anesthetic drugs or other drugs used during operation; (vi) those with severe laryngospasm, massive bleeding or other adverse events during the perioperative period, or 7) those who failed to strictly carry out the trial protocol due to various reasons. This study was approved by the Medical Ethics Committee of our hospital. The gender, age, body weight, body height, ASA grade and Mallampati class had no statistically significant differences between the two groups (P >0.05), and they were comparable (Table 1).

Anesthesia methods

The patients were deprived of food and water for 6 h and 2 h, respectively, before operation. After entering the operating room, the patients were routinely subjected to mask oxygen inhalation and connected to a monitor, and a disposable EEG sensor was placed to monitor the values. Atropine (0.01 mg·kg^{-1}), 5 mg of dexamethasone, midazolam (0.1 mg·kg^{-1}), propofol (3.0 mg·kg^{-1}), fentanyl (2 μg·kg^{-1}) and cis-atracurium (0.1 mg·kg^{-1}) were

Table 1 — Baseline clinical data and Hemodynamic indices

Item	Observation group (n=53)	Control group (n=53)	χ^2/t	P
Clinical data				
Gender (n, %)			0.151	0.697
Male	27 (50.94)	29 (54.72)		
Female	26 (49.06)	24 (45.28)		
Age (years, $\bar{\chi}$±s)	5.83±1.42	5.87±1.50	0.141	0.888
Body wt. (kg, $\bar{\chi}$±s)	21.67±6.29	22.39±6.34	0.587	0.559
Body ht. (cm, $\bar{\chi}$±s)	102.51±13.69	104.07±13.82	0.584	0.561
ASA grade (n, %)			0.155	0.693
Grade I	30 (56.60)	32 (60.38)		
Grade II	23 (43.40)	21 (39.62)		
Mallampati class (n, %)			0.042	0.839
Class I	35 (66.04)	34 (64.15)		
Class II	18 (33.96)	19 (35.85)		
Hemodynamic indices				
MAP (mmHg, $\bar{\chi}$±s)				
T1	74.59±6.75	73.98±6.69	0.467	0.641
T2	77.45±7.36^{a}	79.43±7.51^{a}	1.371	0.173
T3	74.78±6.92*	78.34±7.25^{a}	2.586	0.011
T4	72.43±6.58^{b}*	75.26±6.79^{bc}	2.179	0.032
T5	81.52±7.84^{abcd}*	85.47±8.16^{abcd}	2.541	0.013
HR (beats/min, $\bar{\chi}$±s)				
T1	100.63±10.39	104.96±12.25	1.962	0.052
T2	120.81±13.74^{a}	122.53±13.91^{a}	0.640	0.523
T3	99.61±10.68^{b}*	113.72±12.50^{ab}	6.248	0.000
T4	96.74±9.95^{b}*	100.65±9.89^{abc}	2.029	0.045
T5	100.52±10.15^{b}*	108.24±12.46^{bcd}	3.497	0.001

[^{a}P <0.05 *vs.* T1, ^{b}P <0.05 *vs.* T2, ^{c}P <0.05 *vs.* T3, ^{d}P <0.05 *vs.* T4, and $^{*}P$ <0.05 *vs.* control group]

intravenously injected for anesthesia induction. After muscular relaxation, tracheal intubation was performed under the assistance of a visual laryngoscope. In observation group, propofol (6-8 $mg \cdot kg^{-1} \cdot h^{-1}$) and remifentanil (20-40 $\mu g \cdot kg^{-1} \cdot h^{-1}$) were continuously pumped. In control group, propofol (6-8 $mg \cdot kg^{-1} \cdot h^{-1}$) was continuously pumped, and 0.1% esketamine solution was intravenously infused for maintenance of anesthesia. During operation, the dosage of propofol was adjusted according to entropy index which was kept at 45-55. The pumping volume of propofol was reduced if entropy index was lower than 45, while propofol (0.5 $mg \cdot kg^{-1}$) was added if entropy index was higher than 55. The drugs were withdrawn at 5 min before the end of operation. After the recovery of consciousness, cough reflex and tidal volume in children, the oropharyngeal secretions and blood were sucked clean, and the tracheal catheter was removed. Finally, the children could be sent back to the ward if no adverse reactions such as nausea, vomiting, bucking and dysphoria were found.

Observation indices

The hemodynamic indices mean arterial pressure (MAP) and heart rate (HR) were recorded before anesthesia induction (T1), immediately after intubation (T2), at the beginning of operation (T3), at the end of operation (T4), and at 5 min after extubation (T5). At T1, T2, T3, T4 and T5, fasting venous blood was drawn and centrifuged after coagulation, and the serum was collected for later use. Then the serum C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and epinephrine (E) were detected *via* enzyme-linked immunosorbent assay, and cortisol (Cor) was detected *via* radioimmunoassay. The cluster of differentiation $(CD)^{3+}$ T lymphocytes, CD^{4+} helper T lymphocytes, CD^{8+} inhibitory T lymphocytes and CD^{4+}/CD^{8+} ratio were determined using a FACSCalibur flow cytometer (BD, USA). The anesthetic recovery was observed, and the time of recovery of autonomous respiration and limbs and the duration from anesthetic withdrawal to extubation were recorded. The adverse reactions after extubation were observed.

Statistical analysis

SPSS 19.0 was used for statistical analysis. Quantitative data were expressed as mean±standard deviation ($\bar{\chi}\pm s$). Repeated measures analysis of variance was performed for intergroup comparison at multiple time points. In the case of statistical significance, q test was employed for intergroup comparison at the same time point, while paired *t* test was used for intragroup comparison at two different time points. Numerical data were expressed as case (%), andχ^2 test was performed. $P<0.05$ was considered to be statistically significant.

Results

Hemodynamic indices

In observation group, MAP was significantly higher at T2 than that at T1 (P <0.05), then stayed at a low level until the end of operation, and rose again at T5 and was significantly higher than that at any previous time point (P <0.05). In control group, MAP was significantly higher at T2 than that at T1 (P <0.05), then stayed at a higher level than that at T1 until the end of operation, and also significantly rose again at T5 (P <0.05). MAP had no statistically significant difference between the two groups at T1 and T2 (P >0.05), while it was lower in observation group than that in control group from T3 to T5, showing statistically significant differences (P <0.05).

In observation group, HR was significantly increased at T2 compared with that at T1 (P <0.05), declined at T3 and had no significant difference from T3 to T5 compared with that at T1 (P >0.05). In control group, HR was significantly increased at T2 compared with that at T1 (P <0.05), significantly declined from T3 to T4 (P <0.05), and increased at T5 and had no significant difference from that at T1 (P >0.05). HR had no statistically significant difference between the two groups at T1 and T2 (P >0.05), while it was lower in observation group than that in control group from T3 to T5, showing statistically significant differences (P <0.05) (Table 1).

Inflammatory response indices

The levels of serum CRP, IL-6 and TNF-α in the two groups rose with time, and there were statistically significant differences (P <0.05). Their levels had no statistically significant differences between the two groups at T1 and T2 (P >0.05), while they were lower in observation group than those in control group from T3 to T5, displaying statistically significant differences (P <0.05) (Table 2).

Stress response indices

The levels of serum E and Cor in the two groups gradually rose from T1 to T4 and declined at T5, and there were statistically significant differences at each time point (P <0.05). The levels of serum E and Cor had no statistically significant differences between the

Table 2 — Inflammatory response indices

Item	Observation group (n=53)	Control group (n=53)	*t*	P
CRP (mg/L, $\bar{\chi}\pm s$)				
T1	56.77±6.82	57.03±6.86	0.196	0.845
T2	67.21±7.76 [a]	67.64±7.79 [a]	0.285	0.776
T3	93.58±10.49 [ab*]	114.28±12.53 [ab]	9.222	0.000
T4	116.39±12.87[abc*]	129.57±13.21[abc]	5.203	0.000
T5	134.16±14.08[abcd*]	145.71±15.12[abcd]	4.070	0.000
IL-6 (ng/L, $\bar{\chi}\pm s$)				
T1	26.04±3.25	25.89±3.17	0.241	0.810
T2	32.15±3.79 [a]	31.26±3.68 [a]	1.227	0.223
T3	40.27±4.18 [ab*]	54.32±5.74 [ab]	14.405	0.000
T4	52.38±5.66[abc*]	62.45±6.39[abc]	8.588	0.000
T5	66.52±6.79[abcd*]	73.64±7.46[abcd]	5.139	0.000
TNF-α (ng/L, $\bar{\chi}\pm s$)				
T1	45.82±5.36	46.03±5.41	0.201	0.841
T2	49.76±5.84 [a]	50.11±5.92 [a]	0.306	0.760
T3	56.29±6.45 [ab*]	62.94±6.83 [ab]	5.153	0.000
T4	61.34±6.93[abc*]	67.76±7.15[abc]	4.694	0.000
T5	69.58±7.37[abcd*]	75.29±7.68[abcd]	3.905	0.000

[[a]*P* <0.05 *vs.* T1, [b]*P* <0.05 *vs.* T2, [c]*P* <0.05 *vs.* T3, [d]*P* <0.05 *vs.* T4, and [*]*P* <0.05 *vs.* control group]

two groups at T1 and T2 (P >0.05), while they were lower in observation group than those in control group from T3 to T5, with statistically significant differences (P <0.05) (Table 3).

Immune function indices

At T4 and T5, the levels of CD^{3+}, CD^{4+} and CD^{4+}/CD^{8+} declined, while the level of CD^{8+} rose in the two groups, showing statistically significant differences compared with those at the other three time points (P <0.05), but there were no statistically significant differences between the two groups at each time point (P >0.05) (Table 3).

Anesthetic recovery times

The time of recovery of autonomous respiration and limbs and the duration from anesthetic withdrawal to extubation were significantly shorter in observation group than those in control group, and the differences were statistically significant (P <0.05) (Table 4).

Adverse reactions

Observation group had a lower incidence rate of dysphoria during the recovery period than control group, and the difference was statistically significant (P <0.05). The incidence rates of upper respiratory tract obstruction or apnea, nausea and vomiting had no statistically significant difference between the two groups (P>0.05) (Table 4).

Table 3 — Stress response indices and Immune function indices

Item	Observation group (n=53)	Control group (n=53)	*t*	P
Stress response indices				
E (ng/mL, $\bar{\chi}\pm s$)				
T1	38.96±4.57	40.15±4.73	1.317	0.191
T2	49.78±6.39 [a]	51.07±6.48 [a]	1.032	0.304
T3	61.63±7.82 [ab*]	77.46±8.69 [ab]	9.858	0.000
T4	78.15±8.46[abc*]	85.21±9.64[abc]	4.007	0.000
T5	53.37±5.61[abcd*]	68.39±7.57[abcd]	11.605	0.000
Cor (pg/mL, $\bar{\chi}\pm s$)				
T1	149.52±15.69	151.37±15.86	0.604	0.547
T2	167.38±17.24 [a]	168.92±17.53 [a]	0.456	0.649
T3	182.71±19.45 [ab*]	236.85±24.29 [ab]	12.666	0.000
T4	203.46±20.76[abc*]	272.55±28.41[abc]	14.295	0.000
T5	191.69±19.57[abcd*]	219.43±22.78[abcd]	6.725	0.000
Immune function indices				
CD^{3+} (%, $\bar{\chi}\pm s$)				
T1	51.92±5.83	52.13±5.87	0.185	0.854
T2	50.85±5.76	51.68±5.79	0.740	0.461
T3	51.36±5.81	51.79±5.84	0.380	0.705
T4	43.07±4.42[abc]	42.95±4.36[abc]	0.141	0.888
T5	42.59±4.38[abc]	42.37±4.32[abc]	0.260	0.795
CD^{4+} (%, $\bar{\chi}\pm s$)				
T1	31.78±3.35	32.13±3.42	0.532	0.596
T2	31.54±3.31	31.86±3.37	0.493	0.623
T3	30.92±3.28	30.89±3.25	0.047	0.962
T4	22.16±2.34[abc]	21.92±2.29[abc]	0.534	0.595
T5	21.83±2.27[abc]	21.75±2.24[abc]	0.183	0.855
CD^{8+} (%, $\bar{\chi}\pm s$)				
T1	20.86±2.13	21.05±2.16	0.456	0.649
T2	21.10±2.19	21.32±2.24	0.511	0.610
T3	21.03±2.17	21.28±2.29	0.577	0.565
T4	29.79±3.05[abc]	30.11±3.10[abc]	0.536	0.593
T5	30.25±3.08[abc]	30.15±3.12[abc]	0.166	0.868
CD^{4+}/CD^{8+}				
T1	1.53±0.46	1.54±0.47	0.111	0.912
T2	1.49±0.43	1.50±0.44	0.118	0.906
T3	1.48±0.41	1.47±0.40	0.127	0.899
T4	0.74±0.20[abc]	0.72±0.21[abc]	0.502	0.616
T5	0.72±0.19[abc]	0.71±0.18[abc]	0.278	0.781

[[a]*P* <0.05 *vs.* T1, [b]*P* <0.05 *vs.* T2, [c]*P* <0.05 *vs.* T3, [d]*P* <0.05 *vs.* T4, and [*]*P* <0.05 *vs.* control group]

Table 4 — Anesthetic recovery and adverse reactions

Item	Observation group (n=53)	Control group (n=53)	*t*	P
Time of recovery of autonomous respiration (min, $\bar{\chi}\pm s$)	4.12±1.87	6.93±2.51	6.536	0.000
Time of recovery of limbs (min, $\bar{\chi}\pm s$)	5.03±1.26	8.34±1.42	12.693	0.000
Duration from anesthetic withdrawal to extubation (min, $\bar{\chi}\pm s$)	6.25±1.48	10.72±2.57	10.973	0.000
Adverse reaction				
Dysphoria during the recovery period (n, %)	5(9.43)	19(35.85)	10.557	0.001
Upper respiratory tract obstruction or apnea (n, %)	3(5.66)	9(16.98)	3.383	0.066
Nausea and vomiting (n, %)	7(13.21)	8(15.09)	0.078	0.780

Discussion

Narrow oropharyngeal cavity and fragile mucous membrane in children causes swelling of uvula and surgical cavity and elevation in respiratory resistance in the pharyngeal cavity after low temperature plasma ablation of oral cancer, tonsils and adenoids, leading to a high risk of serious adverse reactions. At present, general anesthesia is adopted in short duration operations, in which it is required to maintain a certain depth of anesthesia during operation, and ensure rapid recovery after operation, without causing delayed respiratory depression and metabolic residues of anesthetic drugs. However, the organ functions of children have not been fully developed, which may affect the metabolism of intravenous anesthetics and lead to residues in the body. Hence, it is important to select appropriate anesthetic drugs. In recent years, propofol has been widely used in clinic. As an alkylphenol intravenous anesthetic, propofol is characterized by fast onset of action, short effectiveness, quick recovery and easily-controlled depth of anesthesia. However, the analgesic effect is poor and the body motion response will be caused when used alone, while increased dosage will lead to suppression of circulatory and respiratory system. Therefore, propofol is often clinically used in combination with other analgesics or local anesthetics[5].

Esketamine is a traditional intravenous anesthetic used in combination with propofol for pediatric surgical anesthesia previously, which is still widely applied in primary hospitals. It is characterized by fast onset of action, small impact on the respiratory system, and a good surface analgesic effect, but repeated use will lead to tolerance and cause many adverse reactions[6]. With the development of anesthesiology, remifentanil (a new generation of opioid receptor agonist) is often used in combination with propofol[7]. Remifentanil can reach blood-brain balance in about 1 min in the human body, and be rapidly degraded by non-specific esterase in the blood and tissues. Therefore, with fast onset of action, short effectiveness, complete elimination and rapid recovery, is suitable for short-duration operations, which causes little damage to liver and kidney functions, and possesses high safety and a potent anesthetic effect[8].

Although the combined use of anesthesia-inducing drugs was reasonable in this study, intubation reactions still occurred in a small number of children, leading to a certain increase in MAP and HR. It is reported in the literature that remifentanil can result in bradycardia and hypotension in a dose-dependent manner, while the adverse reaction of esketamine is elevation of blood pressure[9,10]. In this study, remifentanil (20-40 $\mu g \cdot kg^{-1} \cdot h^{-1}$) combined with propofol was applied for maintenance of anesthesia, and no severe bradycardia and hypotension occurred. Although the changes in MAP and HR were not completely consistent at each time point, the monitored values of MAP and HR in observation group were obviously lower than those in control group after maintenance of anesthesia, consistent with the above literature[9]. Moreover, MAP and HR remained more stable till the end of operation in observation group, consistent with the research results of Unsal *et al.*[11]. A possible explanation is that the side effects of remifentanil are in a dose-dependent manner, and the combination of remifentanil and propofol reduces side effects through lowering their respective dosage. In addition, intravenous pumping can better maintain the stability of plasma drug concentration and effectively control noxious stimuli, thereby stabilize hemodynamics.

It has long been confirmed in a large number of studies that a series of inflammatory and stress responses can be induced by anesthesia and surgical stimulation against the body, and the immune system can also be inhibited. However, the degrees of reactions caused by different anesthetic drugs and methods are quite different[12]. Herein, the results showed that propofol combined with remifentanil could effectively relieve the inflammatory response; consistent with the study of Yuan that remifentanil combined with propofol can reduce the production of inflammatory factors in senile orthopedic surgery[13]. After being transmitted to the nerve center, noxious stimulus signals can stimulate two systems, hypothalamus-pituitary-adrenal cortex and sympathetic-adrenal medulla, leading to the synthesis of adrenal cortex and adrenal medulla, so that the secretion of Cor and E is enhanced. Therefore, serum E and Cor can be used to indicate the body's stress response level[14]. In this study, propofol combined with remifentanil had an inhibitory effect on the stress response, being consistent with a previous literature[15]. The reason is that remifentanil may affect the release of inflammatory factors through interference with the synthesis of prostaglandin. Moreover, it can activate opioid receptors of the central and peripheral nerves,

and reduce the release of C-fiber noxious neurotransmitters, thereby inhibiting the nociceptor sensitization induced by inflammatory mediators, and ultimately easing pain and alleviating inflammatory and stress responses. However, the anesthetic drugs and methods used in this study had little impact on the immune function of children, which was in accordance with the findings of Zhang *et al.*[16]. The time of anesthetic recovery in observation group was significantly shorter than that in control group. One reason is that remifentanil has unique pharmacokinetic characteristics, that is, its metabolism does not rely on liver and kidney functions and is not affected by individual differences, similar to the drug clearance rate in adults. The other reason is that the metabolite of esketamine still possesses 1/5-1/3 of its anesthetic potency and has a longer elimination half-life, which often leads to re-drowsiness after awakening[17]. Furthermore, observation group had an obviously lower incidence rate of dysphoria during the recovery period than control group.The above finding was consistent with related reports that esketamine can lead to such mental symptoms as hallucinations, nightmares, delirium and restlessness during the anesthetic recovery period[18].

Conclusion

The combination of propofol and remifentanil with unique pharmacokinetic and pharmacodynamic characteristics has more advantages in anesthesia for children undergoing low-temperature plasma ablation of oral cancer, tonsils and adenoids. It had more stable hemodynamics, lower levels of inflammatory and stress responses, and showed rapid recovery with fewer adverse reactions. Observatinos of this study support its clinical popularization and application in pediatric operations that require general anesthesia.

Conflict of Interest

Authors declare no competing interests.

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