



Clinical Application of Esketamine Hydrochloride in Children with Emergence Agitation under Sevoflurane Anesthesia

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Objective: To investigate the clinical effect of different doses of esketamine in preventing emergence agitation (EA) in children under sevoflurane general anesthesia.

Methods: 80 children who underwent elective tonsillectomy or (and) adenoidectomy in our hospital were selected. The children were allocated randomly to one of four groups receiving saline (group C), esketamine hydrochloride 0.25 mg/kg (group K0.25), esketamine hydrochloride 0.5 mg/kg (group K0.5) or esketamine hydrochloride 0.75 mg/kg (group K0.75). The children in each group were administered the study drugs 10 minutes before the end of surgery. All children were maintained anesthesia with sevoflurane. The recovery characteristics, including the time to extubation, delivery time from the PACU, postoperative nausea and vomiting, agitation and modified CHEOPS score were recorded and analyzed.

Results: Immediately after extubation, the modified CHEOPS score and postoperative recovery agitation score of the three groups of children receiving intravenous esketamine were lower than those of group C ($P < 0.05$), but there was no statistical difference between the three groups significance ($P > 0.05$). When leaving the PACU, the postoperative awakening agitation scores of the children in the K0.25 and K0.5 groups were lower than those in the C group ($P < 0.05$), but there was no significant difference between the K0.75 and C groups ($P > 0.05$). Compared with group C,

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postoperative extubation time and PACU stay time were significantly prolonged in K0.75 and K0.5 groups ($P < 0.05$).

Conclusions: Low-dose (0.25 mg/kg) of esketamine hydrochloride can reduce the incidence of emergent agitation and postoperative pain, and has little effect on anesthesia recovery.

Keywords: *Esketamine hydrochloride; sevoflurane; children; inhalation anesthesia; emergent agitation.*

1. INTRODUCTION

Pediatric tonsillectomy and adenoidectomy need to be performed in the oral cavity, the operation time is relatively short, and the throat irritation is large, so it needs to be completed under general anesthesia. As an inhalation anesthetic with low blood gas partition coefficient and strong anesthetic efficacy, sevoflurane is one of the commonly used inhalation anesthetics for the induction and maintenance of anesthesia in children. However, during the recovery period of sevoflurane inhalation anesthesia, agitation and delirium often occur, which affects the quality of children's recovery, especially in children undergoing tonsillectomy and adenoidectomy, and even serious adverse events such as airway injury and airway obstruction occur. Some studies have found that ketamine can effectively reduce preoperative separation anxiety and agitation in children, and reduce postoperative pain in children. But high doses of ketamine can have side effects such as hallucinations or nightmares [1-3]. Esketamine hydrochloride is D-ketamine. Compared with ketamine, esketamine hydrochloride has the advantages of strong efficacy, good controllability and fewer side effects [4]. At present, the effect of esketamine hydrochloride in pediatric surgical anesthesia is not clear.

The purpose of this study was to observe the clinical effect of intravenous injection of different doses of esketamine hydrochloride 10 minutes before the end of surgery for the prevention of restlessness during recovery in children under sevoflurane general anesthesia. Whether intravenous injection esketamine hydrochloride can relieve postoperative pain in children and whether it has an effect on anesthesia recovery.

2. MATERIALS AND METHODS

2.1 Normal Information

In this experiment, the sample size was calculated to be 80 cases based on the pre-experiment results. Children who underwent elective tonsillectomy and (or) adenoidectomy in

our hospital from August 2020 to September 2021 were selected, ASA I-II, aged 3-10 years. Children with a history of anesthesia surgery, cardiopulmonary disease, and cognitive or developmental disabilities were excluded. They were divided into four groups by random number table method: control group (group C), different doses of esketamine hydrochloride groups (group K0.25, group K0.5, group K0.75), 20 cases in each group.

2.2 Anesthesia Method

Half an hour before induction of anesthesia, the four groups of children were intramuscularly injected with 0.01 mg/kg atropine. The patient's vital signs (blood pressure, electrocardiogram, oxygen saturation) were closely monitored after admission. Induction of anesthesia: inhalation of 8% sevoflurane and oxygen flow of 5 L/min, intravenous injection of propofol 2 mg/kg, cisatracurium 0.15 mg/kg, and sufentanil 0.2 ug/kg. Endotracheal intubation was performed after the child's consciousness disappeared and muscle relaxation reached the indication for intubation, and mechanical ventilation was performed by connecting to an anesthesia machine. All children were maintained anesthesia by inhalation of 2%-3% sevoflurane and intravenous infusion of 0.1-0.3ug/kg/min remifentanyl, the oxygen flow was maintained at 1.5L/min, and the end-respiratory sevoflurane concentration was maintained at 1.4MAC. The respiratory rate was adjusted reasonably according to the end-tidal carbon dioxide partial pressure of 35 to 45 mmHg. Ten minutes before the end of the operation, group C was given equal volume of normal saline, and group K0.25, group K0.5, and group K0.75 were given intravenous esketamine hydrochloride at the doses of 0.25 mg/kg, 0.5 mg/kg, and 0.75 mg/kg, respectively. At the end of the operation, sevoflurane was stopped, pure oxygen ventilation was changed, and the patient was sent to the PACU. After the operation, the child recovered spontaneously, with choking and swallowing reflexes, and the SpO₂ was above 95%. Then, the tracheal tube was pulled out under close monitoring.

Table 1. Modified CHEOPS method

Score	0	1	2
Cry	No cry	Crying, moaning	Scream
Facial	Smiling	Composed	Grimace
Verbal	Positive	None or other complaints	Pain complaint
Torso	Neutral	Shifting, tense, upright	Restrained
Legs	Neutral	Kicks, squirm, drawn up	Restrained

2.3 Observation Indicator

The age, height, weight, anesthesia time (time from anesthesia induction administration to extubation), operation time, postoperative extubation time (the time from the end of operation to extubation), and PACU stay time were recorded. The occurrence of agitation during recovery was assessed by the same anesthesia nurse who was unaware of the grouping of the children. The modified CHEOPS method (Table 1) [5] was used to record the pain scores of the children immediately after extubation (T1) and at the time of leaving the PACU (T2). When the CHEOPS score was greater than 6 points, intravenous tramadol was administered at 1 mg/kg and the same dose was administered at least 10 minutes apart until the pain was relieved. A 4-point method was used to record the postoperative agitation score immediately after extubation (T1) and when leaving the PACU (T2): 1=quiet, awake, and cooperative; 2=crying and needing comfort; 3=crying, irritability, unable to comfort; 4=disorientation, 3 to 4 points for restlessness during recovery. The 4-point method was also used to record the nausea and vomiting immediately after extubation (T1) and after leaving the PACU (T2): 1= no nausea and vomiting; 2=nausea only; 3= vomiting once; 4=vomiting 2 times or more. The child was returned to the ward with an Aldrete revised score of >9

2.4 Statistical Analysis

SPSS 22.0 statistical software was used to analyze and process the data. The measurement data of age, height, weight, etc. conforming to normal distribution were expressed as mean \pm SD ($\bar{x} \pm s$), and one-way analysis of variance was used. Measurement data that did not conform to normal distribution were expressed as median (M) and interquartile range (IQR), and Kruskal-Wallis test was used. Categorical variables such as gender were tested by chi-square test, EA score and postoperative nausea and vomiting score were tested by Fisher's exact test, $P < 0.05$ indicated a statistically significant difference.

3. RESULTS

Eighty children were included in this study, 20 in each group. There were no significant differences in age, gender, height and weight among the four groups ($P > 0.05$, Table 2).

There was no significant difference in anesthesia time and operation time among the four groups ($P > 0.05$). Compared with group C, the postoperative extubation time and PACU stay time in groups K0.75 and K0.5 were significantly longer ($P < 0.05$). However, there was no significant difference in postoperative extubation time and PACU stay time between group K0.25 and group C ($P > 0.05$). There was no significant difference in postoperative extubation time and PACU stay time among the three groups of children with intravenous esketamine hydrochloride ($P > 0.05$, Table 3).

The modified CHEOPS score immediately after extubation was lower in the three groups of children receiving intravenous esketamine hydrochloride ($P < 0.05$), but there was no significant difference among the three groups ($P > 0.05$). There was no significant difference in the modified CHEOPS score between the four groups of children when they left the PACU ($P > 0.05$). The postoperative recovery agitation scores of the three groups of children receiving intravenous esketamine hydrochloride immediately after extubation were lower than those of group C ($P < 0.05$), but there was no significant difference among the three groups ($P > 0.05$). After leaving the PACU, the postoperative awakening agitation scores of the children in the groups K0.25 and K0.5 were lower than those in the group C ($P < 0.05$). However, there was no significant difference in postoperative recovery agitation scores between the group K0.75 and the group C and between the three groups of children with intravenous esketamine hydrochloride ($P > 0.05$). There was no significant difference in postoperative nausea and vomiting scores between the four groups immediately after extubation and when they left the PACU ($P > 0.05$, Table 4).

Table 2. Comparison of general conditions of four groups of children

Group	Age(yr)	Sex(M:F)	Height (cm)	Weight (Kg)
C (n=20)	6.8 ±2.1	10:10	120.4 ±18.1	24.0 ±6.4
K0.25 (n=20)	6.7 ±1.8	16:4	120.3 ±14.0	24.3 ±6.4
K0.5 (n=20)	5.5 ±1.8	13:7	111.8 ±15.7	22.4 ±6.2
K0.75 (n=20)	6.0 ±2.4	10:10	113.1 ±18.6	20.7 ±6.7

Values are mean ± SD. Group C: administration of normal saline 10 min before the end of the surgery. Group K0.25: administration of ketamine 0.25mg/kg intravenously 10 min before the end of the surgery. Group K0.5: administration of ketamine 0.5 mg/kg 10 min before the end of the surgery. Group K0.75: administration of ketamine 0.75mg/kg intravenously 10 min before the end of the surgery

Table 3. Comparison of anesthesia time, operation time, postoperative extubation time and PACU stay time among four groups of children

Group	Anesthesia time	Operation time	Postoperative extubation time	PACU stay time
C(n=20)	99.5 (80.0~121.3)	57.5 (32.5~73.8)	21.5 (15.0~25.8)	37.5 (31.3~48.8)
K0.25(n=20)	91.0 (70.8~110.0)	50.0 (26.3~62.5)	25.0 (20.0~32.3)	45.0 (36.3~53.8)
K0.5(n=20)	103.5 (81.8~117.8)	50.0 (30.0~65.0)	28.5 (21.3~35.0)*	47.5 (40.0~53.8)*
K0.75(n=20)	85.0 (71.3~100.8)	45.0 (30.0~65.0)	30.0 (25.0~35.0)*	50.0 (41.3~58.8)*

Values are median (M) and interquartile range (IQR). Group C: administration of normal saline 10 min before the end of the surgery. Group K0.25: administration of ketamine 0.25mg/kg intravenously 10 min before the end of the surgery. Group K0.5: administration of ketamine 0.5 mg/kg 10 min before the end of the surgery. Group K0.75: administration of ketamine 0.75mg/kg intravenously 10 min before the end of the surgery.*P < 0.05 compared with the Group C

Table 4. Comparison of modified CHEOPS score, postoperative agitation score, postoperative nausea and vomiting score among four groups of children

Group	Modified CHEOPS score		Postoperative agitation score (1:2:3:4)		PONV score (1:2:3:4)	
	T1	T2	T1	T2	T1	T2
C(n=20)	10.0(8.0~12.0)	7.0 (6.0~8.8)	2:3:15:0	11:9:0:0	17:3:0:0	19:1:0:0
K0.25(n=20)	6.5(6.0~8.8)*	6.0 (6.0~7.0)	12:7:1:0*	18:2:0:0*	19:1:0:0	20:0:0:0
K0.5(n=20)	6.5(6.0~9.5)*	6.0 (6.0~7.0)	11:8:1:0*	17:3:0:0*	19:1:0:0	18:2:0:0
K0.75(n=20)	8.0(6.0~9.8)*	6.0 (6.0~7.0)	12:6:2:0*	13:7:0:0	16:3:1:0	18:2:0:0

Values are median (M) and interquartile range (IQR). Postoperative agitation score: 1=quiet, awake, and cooperative; 2=crying and needing comfort; 3=crying, irritability, unable to comfort; 4=disorientation. PONV (Postoperative nausea and vomiting) score: 1=no nausea and vomiting; 2=nausea only; 3=vomiting once; 4=vomiting 2 times or more. Group C: administration of normal saline 10 min before the end of the surgery. Group K0.25: administration of ketamine 0.25mg/kg intravenously 10 min before the end of the surgery. Group K0.5: administration of ketamine 0.5 mg/kg 10 min before the end of the surgery. Group K0.75: administration of ketamine 0.75mg/kg intravenously 10 min before the end of the surgery.*P < 0.05 compared with the Group C. T1: Immediately after extubation, T2: When leaving PACU

4. DISCUSSION

Sevoflurane, a commonly used inhalation anesthetic for the induction and maintenance of anesthesia in children, has a high incidence of EA during emergence from anesthesia. On the one hand, EA in children is related to children's young age, immature psychological and physical development, and easy fear and anxiety in unfamiliar environments [6]; On the other hand, pain, anesthetics and analgesics are also

important reasons for anesthesia in children with EA.

EA is a manifestation of disturbance of consciousness before awakening after general anesthesia, which is mostly self-limiting and usually resolves spontaneously after the patient's consciousness is fully recovered. EA manifests as both physical and mental symptoms, namely rough movements and emotional agitation. During the agitation process, the risk of

increased heart rate, increased blood pressure, falling out of bed, airway damage, and wound bleeding may occur, and in severe cases, the operation may fail. At the same time, EA will bring difficulties to the management of PACU [7,8]. According to epidemiological research data, the incidence of EA in children is 12% to 13%, especially in preschool children.

At present, many studies have shown that the incidence of EA can be reduced by intravenous injection of propofol [9,10], fentanyl [11], ketamine [12-13], ketorolac [14], and nalbuphine [12], but the etiology and preventive treatment of EA are still unclear. Some studies have also shown that the combination of anesthesia adjuvant and sevoflurane can produce a synergistic effect, the anesthesia effect is good, the postoperative recovery is fast, and it will not cause respiratory depression. The analgesic effect can be maintained for a long time after the operation, and the adverse reactions such as EA and crying in children can be effectively reduced [15].

Ketamine is a racemic mixture of equal amounts of L-ketamine and D-ketamine. Esketamine hydrochloride is D-ketamine, and its pharmacological characteristics are similar to those of racemic ketamine, but it has the advantages of clinical application due to less side effects. Esketamine hydrochloride mainly acts on NMDA receptors, opioid receptors, monoamine receptors, M cholinergic receptors, sodium ion channels and calcium ion channels [16]. Among them, acting on NMDA receptors is the main reason for exerting anesthesia and analgesia. Esketamine hydrochloride's anesthetic, analgesic, and hypnotic intensity is twice that of racemic ketamine, and the dose used to achieve the same anesthetic effect is only 1/2 of the latter. It has been reported that D-ketamine can inhibit the hyperalgesia caused by the sudden discontinuation of opioids, reduce postoperative pain, prolong the time of postoperative analgesia, and have no significant effect on breathing and circulation [17, 18]. Some studies have found that intravenous injection of 0.25 mg/kg ketamine 10 minutes before the end of surgery can reduce the occurrence of EA in sevoflurane general anesthesia, and will not affect postoperative recovery [19]. Dalens et al [20] reported that intravenous injection of ketamine 0.25 mg/kg or nalbuphine 0.1 mg/kg could effectively prevent the occurrence of EA in children undergoing general anesthesia with MRI.

This study found that children who received intravenous esketamine hydrochloride had lower postoperative pain levels and the incidence of EA, suggesting that esketamine hydrochloride has a good analgesic effect and can prevent the occurrence of EA. When comparing three different doses of esketamine hydrochloride, we found that pain scores were reduced in all children immediately after extubation, but there was no statistical difference between the different dose groups. On leaving the PACU, we found lower postoperative agitation scores in the groups K0.25 and K0.5, but the group K0.5 did not further reduce the incidence of EA, and the postoperative extubation time and PACU stay time in the group K0.5 were longer than those in the control group and group K0.25. For the group K0.75, we found that although it could reduce postoperative pain, there was no difference in the wake-up agitation score when leaving the PACU and the control group, and it could significantly prolong the postoperative extubation time and PACU stay time.

Although this study found that group K0.25 can reduce the incidence of EA without prolonging postoperative extubation time and PACU stay time, this study has certain limitations, the sample size of this study is relatively small, and the research object is children aged 3-10 years, and does not include the entire age span of children, so the results of the study cannot be used for children of all ages. In order to obtain more accurate research results, it is necessary to further expand the sample size and conduct research with more age groups.

5. CONCLUSION

Low-dose (0.25 mg/kg) esketamine hydrochloride can reduce the incidence of EA and relieve postoperative pain, has little effect on extubation time and PACU stay time, and has few adverse reactions, which is worthy of clinical application.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the product because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. The funds required for this study were provided by Hospital Pharmacy Research

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ETHICAL APPROVAL AND CONSENT

This study was approved by the ethics committee of our hospital (KJ2020008), and informed consent was signed with the guardians of the children.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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