Clinical Trial/Experimental Study

Medicine

OPEN

Effects of preoperative nasal spray esketamine on separation anxiety and emergence agitation in pediatric strabismus surgery

A randomized clinical trial

Wei Liu, MM[a], Ruiqiang Sun, MD[a], Xuesong Gao, MM[a], Shuzhen Wang, MM[a]

Abstract

Objective: To investigate the effects of preoperative nasal spray esketamine on separation anxiety and postoperative emergence agitation in pediatric strabismus surgery.

Method: Ninety children aged 3 to 6 years who underwent elective strabismus surgery were randomly divided into 3 groups that received 0.5 mg/kg (group S_1), 1 mg/kg of esketamine (group S_2), and the same volume of normal saline (group C) by nasal spray 10 minutes before surgery. The observation indicators of this test include the Ramsay sedation score, separation anxiety score, mask induction score, and the incidences of postoperative emergence agitation. Patient's heart rate, blood oxygen, post anesthesia care unit stay time, and any adverse events were recorded.

Results: The Ramsay sedation score was significantly lower in group C than those in groups S_1 and S_2 ($P < .001$). The separation anxiety scores and the mask induction scores were significantly higher in group C than those in groups S_1 and S_2 ($P < .001$). The incidences of emergence agitation in groups S_1 and S_2 were significantly lower than that in C group ($P < .001$). No obvious clinical complication was observed.

Conclusion: Preoperative nasal spray esketamine reduced the preoperative separation anxiety and decrease emergence agitation in pediatric strabismus surgery.

Abbreviations: PACU = post anesthesia care unit, PAED = pediatric anesthesia emergence delirium.

Keywords: emergence agitation, nasal spray esketamine, pediatric strabismus surgery, separation anxiety

1. Introduction

Strabismus in children affects both appearance and visual development, and thus early surgical corrective intervention is very important.[1] Although this surgical correction is relatively small, it is usually carried out under general anesthesia because preschool children often cannot cooperate with the surgeons. Preschool children are highly dependent on their parents, so they often show separation anxiety and even cry when separated from parents. Studies have shown that approximately 65% to 80% of children experience preoperative anxiety.[2,3] Furthermore, children with preoperative anxiety are 3 times more likely to have delirium, nightmares, separation anxiety, sleep disorders, night crying, enuresis, temper tantrum, apathy, withdrawal, eating disorders, attacking authority, and negative behavior changes (such as increased fear of medical staff), which has a long-term negative impact on children's future medical interactions and hinder their normal growth and development.[4] The incidence of postoperative agitation in pediatric ophthalmology is significantly higher than that in other surgical interventions, which may be caused by factors such as postoperative eye patches or bandages; preoperative anxiety is also 1 of the causes of postoperative agitation.[5]

Many kinds of anesthetic adjuvants, including sedatives and analgesics, have been effectively used to reduce preoperative anxiety and postoperative agitation, such as sufentanil, midazolam, propofol, ketamine, dexmedetomidine.[6] However, due to their properties, these drugs may cause adverse reactions, leading to delayed awakening, respiratory depression, or nausea and vomiting. Therefore, an anesthetic was needed that not only reduces the preoperative separation anxiety of children, and decreases the occurrence of agitation, but also does not have side effects such as respiratory depression, prolong the recovery time.

Esketamine has sedative and analgesic activities; it is very easily absorbed through the mucosa, with minor mucosal irritation. Hence, this nasal spray has the advantages of rapid effect and easy acceptance by children.[7] Therefore, we hypothesized

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] *Department of Anesthesiology, Tianjin Eye Hospital, Tianjin, China.*

** Correspondence: Ruiqiang Sun, Department of Anesthesiology, Tianjin Eye Hospital, 4 Gansu Road, Tianjin 300020, China (e-mail: 38940444@qq.com).*

How to cite this article: Liu W, Sun R, Gao X, Wang S. Effects of preoperative nasal spray esketamine on separation anxiety and emergence agitation in pediatric strabismus surgery: A randomized clinical trial. Medicine 2022;101:51(e32280).

Received: 25 October 2022 / Received in final form: 19 November 2022 / Accepted: 23 November 2022

http://dx.doi.org/10.1097/MD.0000000000032280

that preoperative nasal spray administration of esketamine can reduce preoperative separation anxiety and the incidence of postoperative agitation in children.

2. Patients and Methods

2.1. Patients

The research was approved by Ethics Committee of Tianjin Eye Hospital. The study was registered in the Chinese Clinical Trial Registry under the number ChiCTR2100045441 and first registration date April 15, 2021. The trial included 90 children aged 3 to 6 years with american society of anesthesiologist physical status I and II who underwent elective strabismus surgery. Permission for inclusion was obtained from the parents, and an informed consent form was signed. The exclusion criteria were as follows: moderate upper tract infection, neurologic illness, behavioral abnormality, parental refusal, other contraindications to the use of esketamine.

2.2. Random grouping and blinding

Randomization grouping was applied of 96 screened children, 16 of which withdrew from the trial. Finally, using a computer-generated randomization program, we randomized and divided the remaining 90 children into 3 groups: groups C, S_1, and S_2, The flow chart of the process of subject inclusion is presented in Fig 1. The patients, guardians and the anesthesiologist who conducted the nasal spray treatment were blinded to reduce bias.

2.3. Protocols of nasal spray esketamine treatments

The specification of esketamine used in this test was 50 mg/2 mL, with an initial concentration of 25 mg/mL. The children in group S_2 were treated with undiluted esketamine stock solution, whereas the children in group S_1 received 12.5 mg/mL of esketamine diluted twice with normal saline. Finally, the volume of the nasal spray received by each group was 0.4 mL/kg. Patients in group accepted the same volume of sterile normal saline. Esketamine or saline were sprayed into the nostrils of the children, accompanied by their parents, 10 minutes before anesthesia induction.

2.4. Anesthesia induction and maintenance

An intravenous indwelling needle was placed with the parents the night the before operation to reduce the adverse stimulation of preoperative venipuncture to children. Solid food was forbidden for 8 hours, formula milk was forbidden for 6 hours and sugar water was forbidden for 2 hours before operation. All children were given 0.01 mg/kg penehyclidine hydrochloride intramuscularly 30 minutes preoperatively to reduce oral and respiratory secretions. Patients separation anxiety score (Table 1) and sedation scores (Table 2) were recorded after the children entered the operation alone and separated from their parents. Anesthesia induction was performed using a mask with 6% sevoflurane and an oxygen flow of 5 L/minutes. The degree of mask acceptance was recorded by anesthesiologists who did not know the preoperative drug grouping based on a modified 3-point scale (1 = calm, cooperative or asleep; 2 = moderate

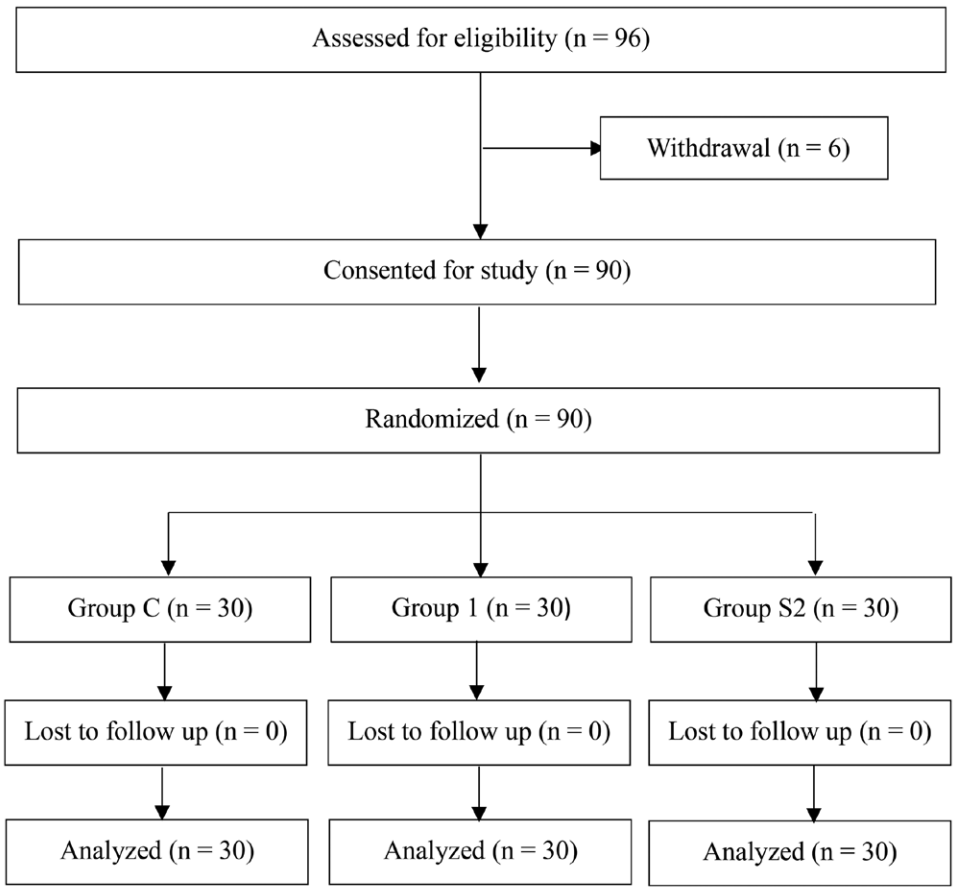

Figure 1. CONSORT diagram showing the flow of participant recruitment throughout each stage of the randomized trial. Patients in group *S*1 intranasally spray esketamine received 0.5 mg/kg, the patients in group *S*2 intranasally spray esketamine received 1 mg/kg, and patients in group C received the same volume of normal saline.

Table 1

Separation anxiety score.

Score	Performance
1	Clam
2	Not smiling, tentative behavior, cooperation with separation
3	Crying
4	Thrashing, crying with movements with arms and legs, resisting

Table 2

Ramsay sedation score.

Score	Performance
1	Patient is anxious and agitated or restless, or both
2	Patient is cooperative, calm and well oriented
3	Patient responds to commands only
4	Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5	Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6	Patient exhibits no response

fear of the mask, cooperative with reassurance; and 3 = combative, crying).[8,9] A child that struggled and cried seriously during mask induction was recorded to have a score of 3 and was regarded as dissatisfied with the preoperative medication, and intravenous propofol of 1 mg/kg was given immediately as a remedy. The mask acceptance score of 1 to 2 was considered to be effective for this nasal spray.

We inserted the reinforced flexible laryngeal mask airway after the patient's jaw had relaxed and the throat reflex had disappeared. Sufentanil 0.1 to 0.2 ug/kg was then given intravenously for intraoperative analgesia, and 2 to 4 drops of a local anesthetic were instilled in the conjunctiva for intraoperative analgesia before the operation. Intraoperative anesthesia maintenance combined intravenous and inhalation anesthesia with intravenous infusion of propofol 2 to 4 mg/kg/hours, and inhalation of 3% to 4% sevoflurane. No muscle relaxants were administered during the whole anesthesia process, and the patient kept spontaneous breathing throughout the whole process. Routine intraoperative monitoring included electrocardiogram, blood pressure, heart rate, pulse oxygen saturation respiratory rate, tidal volume, end-tidal carbon dioxide, end respiratory sevoflurane concentration, and minimum alveolar concentration value. In case of respiratory depression during the operation, prompt auxiliary ventilation was to be given to maintain end-tidal CO_2 pressure levels between 35 and 50 mm Hg. We closed the sevoflurane volatilization tank after operation and increased the oxygen flow to 6 L/minutes to eliminate sevoflurane from breathing. Patients were transferred with laryngeal mask airway to the post anesthesia care unit (PACU) with adequate spontaneous ventilation.

2.5. Protocols for PACU

After the children were transferred to PACU, their blood pressure, heart rate, and blood oxygen saturation were continuously monitored. They were kept warm by a heating blanket and evaluated every 5 minutes. After the children woke up, the nurse PACU prevented them from falling into bed and comforted them gently. The scores of children were continuously assessed using the pediatric anesthesia emergence delirium (PAED) scale[10] and the children's hospital of eastern ontario pain scale scores,[11] and the maximal scores obtained were recorded. The evaluation standard of postoperative agitation was PAED scores > 10. Intravenous propofol (1 mg/kg) had to be given immediately for sedation as a remedial measure in case the score exceeds 15. All adverse incidents, including, but not limited, to respiratory depression, postoperative nausea or vomiting, and laryngospasm, were recorded.

2.6. Statistical analysis

In this study, we adopted the separation anxiety score as the main observation end point. Through a pilot study (unpublished), we obtained the mean separation anxiety scores of the 3 groups (n = 8), which were 1.8, 1.3, and 2.8, respectively, and the standard deviation values, which were 0.6, 0.5, and 0.6, correspondingly. At $\alpha = 0.05$ and $\beta = 0.1$, the sample size calculated by the sample size calculation formula of the multigroup mean comparison was 18 cases, and the sample size of each group was 27, based on the 50% shedding rate of each group.

Data are presented as mean ± SD, median (range), or number (%), quantitative data were analyzed by 1-way analysis of variance and qualitative data were analyzed by chi square analysis. SPSS statistical software for Windows, version 21.0, was used for all statistical analyses. $P < .05$ was considered to indicate a statistically significant difference.

3. Results

3.1. General characteristics of the participants

In this trial, we initially recruited 96 participants, and finally 90 subjects were included based on the exclusion criteria (Fig.1). Eventually, using a computer-generated randomization program, we randomized and divided 90 children into 3 groups, groups C, S_1, and S_2, which received different dosages of nasal spray treatments with normal saline or esketamine. We collected data and assessed the general conditions of the patients, including weights, the ages, American Society of Anesthesiologists physician status, ratios of sex, and duration of anesthesia and surgery. There was no statistical difference in the above indexes among the 3 groups (Table 3).

3.2. Ramsay sedation, separation anxiety, and mask induction scores

Patients were sedated and easily separated from parents without cry after nasal esketamine treatment in groups S_1 and S_2. In contrast, no sedative effect was observed in children with normal saline spray treatment in group C. The Ramsay sedation score in group C was significantly lower than those in groups S_1 and S_2 ($P < .001$). The separation anxiety scores in groups S_1 and S_2 were significantly lower than that in group C ($P < .001$). The patients who received nasal spray esketamine showed more cooperation for mask induction. The mask acceptance scores in groups S_1 and S_2 were significantly lower than that in group ($P < .001$; Table 4);

3.3. Postoperative emergence agitation

The evaluation criteria of postoperative emergence agitation in this study was a PAED score greater than 10. We found that the pretreatment with different dosages of nasal spray esketamine significantly decreased the incidence of emergence agitation as compared with the group C, the number of postoperative emergence agitation in each group were (7 in group S_1 and 4 in group S_2 versus 18 in group C, $P < .001$; Table 5). Furthermore, the PAED scores were consistent with the above results; they were

statistically significantly lower in groups S_1 and S_2 were than in group C ($P < .001$ Table 5).

3.4. Adverse events

The nasal spray of esketamine did not prolong the time of PACU. As can be seen in Table 3, no statistical difference in PACU stay time was present among the 3 groups (Table 5). Although the heart rates of the children in the S_1 and S_2 groups were faster than that of the children in group (Table 6), the times of acceleration had no clinical significance and did not need special drug treatment. There was no respiratory depression during preoperative sedation in the 3 groups. We observed that the whole course of blood oxygen in the 3 groups was more than 97%. No nausea, vomiting, or laryngospasm occurred in the children in the operating room.

4. Discussion

The study confirmed that nasal spray esketamine not only reduced preoperative separation anxiety but also decreased the high incidence of postoperative emergence agitation in preschoolers who underwent general anesthesia with sevoflurane for strabismus surgery. Moreover, the main advantage of esketamine treatment was that nasal spray was easily accepted by the children and acted quickly. There were no side effects, such as respiratory depression and prolonged PACU stay time.

Preschool children often experience anxiety, fear, and even cry, and frequently refuse to be separated from parents.[2,12] This might have important implications as the implementation of anesthesia induction and anesthesia quality may exert negative effects and lead to the occurrence of emergence agitation in children with preoperative adverse separation memories.[13,14] In more serious cases, mental trauma, fear, urinary incontinence, depression, anxiety, and other sequelae may be caused. Therefore, it is meaningful to reduce the separation anxiety before anesthesia in children that undergo strabismus surgery.

Esketamine, a dextral ketamine isomer, has 2-fold higher anesthetic potency than racemic ketamine and produces less psychomimetic side effects.[15] The antidepressant effect of esketamine nasal spray has been extensively examined in recent years, but few studies have been conducted on the application of esketamine nasal spray for preoperative sedation in children. Therefore, we investigated the effects of esketamine nasal spray in pediatric patients undergoing strabismus ophthalmic surgery. Previously, Xin[16] compared the effects of dexmedetomidine and esketamine in pediatric dentistry surgery. The sedation onset time of esketamine (0.5 mg/kg) was significantly shorter compared than that of dexmedetomidine (1 and 1.5 μg/kg). In the present experiment, we observed that the onset time is 5 to 10 minutes after nasal spray, which was faster than dexmedetomidine surgery as previously reported by Cimen.[17]

Sevoflurane inhalation anesthesia induction and laryngeal mask to maintain spontaneous breathing is a very suitable anesthesia scheme for pediatric strabismus surgery.[18] Although sevoflurane does not stimulate the respiratory tract, many children frequently resist sevoflurane mask induction due to the unpleasant smell. Moreover, the distressing experience induced by anesthesia induction has been revealed to have impact on postoperative emergence agitation when waking up. Therefore, it is necessary to give appropriate sedation before anesthesia induction.[5] A study on anesthesia induction in children indicated that preoperative sedation with esketamine 1 mg/kg could improve the satisfaction of anesthesiologists in inhalation induction.[19] Based on our research findings, we reached similar conclusions. We found that esketamine nasal spray provided adequate sedation effect for pediatric patients undergoing inhalational mask induction, and nasal spray esketamine (0.5 or 1 mg/kg) significantly reduced the mask scores as compared with those in group C. The quality of anesthesia induction was improved.

Postoperative emergence agitation is very common in children under sevoflurane general anesthesia, and the incidence of ophthalmic surgery is higher.[20] Postoperative pain is often considered to be 1 of the main causes of postoperative agitation[21]; however, due to slighter surgical stimulation and the application

Table 3

Demographic, surgical, and anesthesia data.

	*S*1 group, esketamine 0.5 mg/kg	*S*2 group, esketamine 1 mg/kg	C group, normal saline	*P* value
Age (yr)	4 (3, 6)	4 (3,6)	5 (3, 6)	.741
Weight (kg)	15.77 ± 2.33	16.47 ± 1.67	16.04 ± 1.56	.562
ASA 1/2	30	30	30	
Duration of anesthesia (min)	33.38 ± 4.86	34.18 ± 3.28	32.42 ± 2.16	.683
Eyes operated, 1/2	20/10	19/11	17/13	.618

Data are presented as mean ± SD, median (IQR) or number of patients. None of these parameters differed significantly among the three groups.
ASA = american society of anesthesiologists.

Table 4

Ramsay sedation, separation anxiety, and mask induction scores.

	S1 group, esketamine 0.5 mg/kg	S2 group, esketamine 1 mg/kg	C group, normal saline	P value
Ramsay sedation score	3.2a ± 0.2	3.5a ± 0.4	1.3 ± 0.3	< .001
Separation anxiety score	1.8a ± 0.6	1.3a ± 0.4	2.8 ± 0.5	< .001
Mask induction score	1.5a ± 0.2	1.2a ± 0.2	2.8 ± 0.1	< .001

Data are presented as mean ± SD.
Compared with group C.
[a] $P < .05$.

Table 5

Incidence of emergence agitation, PAED scale score and CHEOPS score.

	*S*1 group, esketamine 0.5 mg/kg	*S*2 group, esketamine 1 mg/kg	C group, normal saline	*P* value
Incidence of emergence agitation	7 (23%)a	4 (13%)a	18 (60%)	< .001
PAED scale score	7.26a ± 0.76	5.23a ± 0.61	15.36 ± 0.85	< .001
CHEOPS score	2.13 ± 0.24	2.09 ± 0.36	2.25 ± 0.46	.921
PACU stay time(min)	28.34 ± 5.62	29.33 ± 4.20	28.52 ± 5.11	.650

Data are presented as mean ± SD or number (%).
CHEOPS = children's hospital of eastern ontario pain scale, PAED = pediatric anesthesia emergence delirium, PACU = post anesthesia care unit.
Compared with group C.
[a] $P < .05$.

Table 6

HR before nasal spray, after nasal spray (5 and 10 min) in the three groups.

	*S*1 group, esketamine 0.5 mg/kg	*S*2 group, esketamine 1 mg/kg	C group, normal saline	*P* value
*T*1 (baseline)	114 ± 5.3	113 ± 6.8	115 ± 6.2	.748
*T*2 (5 min)	118 ± 3.8	120a ± 4.1	123a ± 4.8	<.001
*T*3 (10 min)	116 ± 3.9	124a ± 4.2	126a ± 3.1	<.001

Data are presented as mean ± SD.
Compared with group C.
[a] $P < .05$.

of local anesthetics, the severity of postoperative pain after strabismus surgery is relatively low, with a VAS score ranging from 1 to 2.[22] There was no difference in the children's hospital of eastern ontario pain scale scores among the 3 groups in our study. We speculate that the main causes of postoperative emergence agitation are the use of sevoflurane and postoperative visual field occlusion. A single dose or continuous infusion of ketamine was previously reported showed to reduce the emergence agitation after sevoflurane treatment of children.[23] Interestingly, we established that a single dose of esketamine spay prior to induction can also suppress postoperative emergence agitation without prolonging the emergence time.

Furthermore, we found that 0.5 or 1 mg/kg nasal spray of esketamine caused no respiratory depression and can thus be safely used for preoperative sedation in children. We observed that the whole time-course of blood oxygen saturation in the 3 groups was more than 97%. There are some limitations in our study. No midazolam or dexmedetomidine treatment group was established to compare the effects with those esketamine treatment in preschoolers.

In conclusion, nasal spray esketamine 0.5 or 1 mg/kg significantly reduced separation anxiety and decreased the incidence of postoperative emergence agitation in pediatric strabismus surgery.

Author contributions

Data curation: Xuesong Gao, Shuzhen Wang.
Formal analysis: Ruiqiang Sun, Xuesong Gao, Shuzhen Wang.
Methodology: Wei Liu, Ruiqiang Sun.
Investigation: Xuesong Gao, Shuzhen Wang.
Software: Wei Liu.
Writing – original draft: Wei Liu.
Writing – review & editing: Wei Liu, Ruiqiang Sun.

References

[1] Dotan G, Qureshi HM, Nelson LB. Instructions to patients and families following strabismus surgery. J Pediatr Ophthalmol Strabismus. 2015;52:142–6; discussion 141.
[2] Tobias JD. Preoperative anesthesia evaluation. Semin Pediatr Surg. 2018;27:67–74.
[3] Dreger VA, Tremback TF. Management of preoperative anxiety in children. AORN J 2006;84: 778–80, 782–6, 788–90, passim; quiz 805–808.
[4] Ahmed MI, Farrell MA, Parrish K, et al. Preoperative anxiety in children risk factors and non-pharmacological management. Middle East J Anaesthesiol 2011;21:153–64.
[5] Dahmani S, Delivet H, Hilly J. Emergence delirium in children: an update. Curr Opin Anaesthesiol. 2014;27:309–15.
[6] Kim MS, Moon BE, Kim H, et al. Comparison of propofol and fentanyl administered at the end of anaesthesia for prevention of emergence agitation after sevoflflurane anaesthesia in children. Br J Anaesth. 2013;110:274–80.
[7] Peltoniemi MA, Hagelberg NM, Olkkola KT, et al. Ketamine: a review of clinical pharmacokinetics and pharmacodynamics in anesthesia and pain therapy. Clin Pharmacokinet. 2016;55:1059–77.
[8] Keles S, Kocaturk O. Comparison of oral dexmedetomidine and midazolam for premedication and emergence delirium in children after dental procedures under general anesthesia: a retrospective study. Drug Des Devel Ther. 2018;12:647–53.
[9] Lin Y, Chen Y, Huang J, et al. Efficacy of premedication with intranasal dexmedetomidine on inhalational induction and postoperative emergence agitation in pediatric undergoing cataract surgery with sevoflurane. J Clin Anesth. 2016;33:289–95.
[10] Sikich N, Lerman J. Development and psychometric evaluation of the pediatric anesthesia emergence delirium scale. Anesthesiology. 2004;100:1138–45.
[11] Honarmand A, Safavi MR, Jamshidi M. The preventative analgesic effect of preincisional peritonsillar infifiltration of two low doses of ketamine for postoperative pain relief in children following adenotonsillectomy.
[12] Dave NM. Premedication and Induction of anaesthesia in paediatric patients. Indian J Anaesth. 2019;63:713–20.
[13] Wang Y, Chu LY, Wang SS, et al. [Preoperative video distraction alleviates separation anxiety and improves induction compliance of preschool children: a randomized controlled clinical trial]. Zhonghua Yi Xue Za Zhi. 2021;101:2066–70.
[14] Yuki K, Daaboul DG. Postoperative maladaptive behavioral changes in children. Middle East J Anaesthesiol. 2011;21:183–9.
[15] Doenicke A, Kugler J, Mayer M, et al. Ketamine racemate or S- (+)-ketamine and midazolam. The effect on vigilance, efficacy and subjective findings (German). Anaesthesist. 1992;41:610–8.
[16] Xin N, Xu H, Yue C. Comparison between dexmedetomidine and esketamine in pediatric dentistry surgery. Transl Pediatr. 2021;10:3159–65.
[17] Cimen ZS, Hanci A, Sivrikaya GU, et al. Comparison of buccal and nasal dexmedetomidine premedication for pediatric patients. Paediatr Anaesth. 2013;23:134–8.
[18] Peng A, Dodson KM, Thacker LR, et al. Use of laryngeal mask airway in pediatric adenotonsillectomy. Arch Otolaryngol Head Neck Surg. 2011;137:42–6.
[19] Lu X, Tang L, Lan H, et al. A Comparison of intranasal dexmedetomidine, esketamine or a dexmedetomidine-esketamine combination for induction of anaesthesia in children: a randomized controlled double-blind trial. Front Pharmacol. 2022;12:808930.
[20] Heinmiller LJ, Nelson LB, Goldberg MB, et al. Clonidine premedication versus placebo: effects on postoperative agitation and recovery time in children undergoing strabismus surgery. J Pediatr Ophthalmol Strabismus. 2013;50:150–4.
[21] Ozcan A, Kaya AG, Ozcan N, et al. Effects of ketamine and midazolam on emergence agitation after sevoflflurane anaesthesia in children receiving caudal block: a randomized trial. Rev Bras Anestesiol. 2014;64:377–81.
[22] Henzler D, Kramer R, Steinhorst UH, et al. Factors independently associated with increased risk of pain development after ophthalmic surgery. Eur J Anaesthesiol. 2004;21:101–6.
[23] Jeong WJ, Kim WY, Moon MG, et al. The effect of ketamine on the separation anxiety and emergence agitation in children undergoing brief ophthalmic surgery under desflurane general anesthesia. Korean J Anesthesiol. 2012;63:203–8.