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The effect of intravenous ketamine versus thiopental in the preoperative holding area on the separation anxiety and emergence agitation in children

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Abstract: Background: Pre-anesthetic medication is often required in children to provide anxiolysis and to lessen the psychological impact of hospitalization and procedures. In this study, we compared the effects of intravenous ketamine versus thiopental on the separation anxiety and emergence agitation in children undergoing tonsillectomy/adenoidectomy. Methods: Eighty-two children aged 2-8 years scheduled for adenotonsillectomy were enrolled in this prospective double-blind, randomized study. The children were divided into two groups to receive either intravenous ketamine 1 mg/kg (Group K) or thiopental sodium 3 mg/kg (Group T) to facilitate separation from their parents in the preoperative holding area. Anesthesia was induced using 5 mg/kg thiopental sodium in group K and 2 mg/kg in group T, and was maintained using sevoflurane. The separation anxiety score, emergence agitation score, time from stopping the anesthetics to eye opening, extubation time, and postoperative nausea and vomiting were assessed. Results: There were no significant differences between groups K and T in the preoperative separation anxiety score, emergence agitation score and postoperative nausea and vomiting. However, time to eye opening from stopping the anesthetics and extubation time were significantly delayed in group K compared with group T. Conclusions: Intravenous ketamine or thiopental in the preoperative holding area are equally effective decreasing anxiety upon separation from parents and may not affect incidence of emergence agitation. The administration of thiopental used to induce anesthesia appears to be a better choice for preanesthetic medication with careful monitoring.

Keywords: Agitation, Children, Ketamine, Separation Anxiety, Thiopental

1. Introduction

The preoperative period can be a stressful time for children and their parents. In fact, approximately 40-60 % of children experience anxiety regarding an impending surgical experience [1]. Preoperative anxiety in children may induce preoperative and postoperative complications. Elevated levels of preoperative anxiety have been found to be associated with difficulty in anesthetic induction and development of postoperative maladaptive behavioral changes [2,3]. Difficult separation of children from their parents is associated with a higher risk of developing postoperative delirium [4].

In children pre-anesthetic medications are frequently administered as pharmacological adjunctions to help alleviate the stress and fear of surgery as well as to ease child parental separation and promote a smooth induction. An ideal preanesthetic medication should ease separation from parents and facilitate patient acceptance of the face mask during induction of anesthesia without prolonging emergence, increasing cardiopulmonary instability, or postoperative delirium, nausea and vomiting. Oral, rectal, intranasal, intravenous and intramuscular routes have been used. However, each route has its own disadvantages. Pre-anesthetic medication administered intravenously for a rapid onset have made it a convenient way to pre-medication.

Thiopental sodium is commonly used for the induction of anesthesia in pediatric patients. However, the efficacy of thiopental for premedication in children has not been compared with that of intravenous ketamine.

The purpose of this study was to compare the effect of intravenous injection of ketamine or thiopental as premedication in the preoperative holding area. The effect of ketamine or thiopental was measured by the separation anxiety score, emergence agitation score, and side effects in children undergoing tonsillectomy/adenoidectomy.

2. Methods

The study was performed a receiving approval from the Institutional Review Board and informed consent of patients and guardians following detailed explanation of the purpose and the procedure of this study. Eighty-two children, between the ages 2-8 years, classified as American Society of Anesthesiologists physical status I who were scheduled to undergo tonsillectomy and endoscopic adenoidectomy under general anesthesia, were enrolled into this study. Children with a history of sleep apnea, developmental delay, psychological disorders, or any neurological disorder were excluded.

Atropine 0.01 mg/kg was injected intramuscularly 30 min before the induction of anesthesia. The patients were randomly allocated to two groups. Group K (n = 42) received 1.0 mg/kg of intravenous ketamine and group T (n = 42) received 3.0 mg/kg of intravenous thiopental sodium in the preoperative holding area. All medications were administered by personnel who were not involved in the study and the total injection volume of medications was 6 ml. After the patients became unconscious, they were taken to the operating room immediately following their separation from their parents. Separation anxiety score was assessed on a simple 4-point scale as follows: 1, calm child: no kind of intervention; 2, consolable child: requires only physical contact with parents; 3, agitated child: a screaming and crying child; and 4, aggressive child: must be physically restrained to avoid harm [4]. Patients with monitoring the oxygen saturation were transferred to the operation room. Vital signs were monitored and recorded throughout the study. Standard monitoring included ECG, blood pressure, and pulse oximetry. Group K received thiopental sodium 5 mg/kg and group T received thiopental sodium 2 mg/kg intravenously. Rocuronium 0.6 mg/kg and fentanyl 1.0 ug/kg were administered intravenously, and an endotracheal intubation was performed. Anesthesia was maintained with oxygen 2.0 L/min, nitrous oxide 2.0 L/ml and sevoflurane at 1.5 – 2.0 vol%. Controlled ventilation was performed to maintain end-tidal CO_2 between 35 and 40 mmHg. At the end of surgery, administration of sevoflurane and nitrous oxide was discontinued and then manual ventilation was performed with 100% oxygen at 6 L/min. To reverse residual muscle relaxation, pyridostigmine 0.2 mg/kg and glycopyrrolate 0.008 mg/kg were administered. Operation time, anesthesia time (the time from the induction of anesthesia to tracheal extubation), time from stopping the anesthetics to eye opening with verbal stimuli, and extubation time (the time from the end of surgery to tracheal extubation) were recorded. Patients were extubated when awake and certain clinical criteria were met (purposeful movement, regular breathing, swallowing), placed in the recovery position, and transported to the post-anesthesia care unit (PACU).

In the PACU, one anesthesiologist who was blinded to the patient group evaluated emergence agitation using a four-point scale (1, calm; 2, not calm but could easily be calmed; 3, moderately agitated or restless; 4, combative, excited, or disoriented) [5]. For evaluation of postoperative nausea and vomiting, a 4-point scale was employed to check the incidence of adverse events as follows: 1, none; 2, nausea only; 3, one episode of vomiting; 4, more than 2 episodes of vomiting. Recurrent vomiting within 5 minutes was regarded as one single episode. Ondansetron 0.15 mg/kg was used as an antiemetic drug and if the vomiting was not controlled, repeated administration was performed up to a total dose of 4 mg.

Differences if the incidence of emergence agitation was primary variables for power analysis. We estimated that 42 patients were required in each group to detect a difference of 30% in the incidence of emergence agitation in the group K with a power of 0.8 and α of 0.05. We assumed that the incidence of emergence agitation in the group T would be 60% based on a previous study [6]. The data were expressed as mean ± standard deviation or number (%). The continuous variables were compared between two groups by using the independent T-test. Categorical variables were compared using the chi-square test or Fisher's exact test as appropriate. Statistical analysis was performed using IBM SPSS 21.0 (SPSS Inc., Chicago, IL, USA). P values less than 0.05 were considered statistically significant.

3. Results

There was no statistically significant difference in the demographic data (Table 1). However, the time from stopping the anesthetics to eye opening and extubation time were significantly delayed in group K compared to group T. There was no statistically significant difference in the duration of recovery room stay between the two groups (Table 2). None of the patients developed hypotension, bradycardia, or hypoxemia (oxygen saturation < 95%) during the time from the administration of preoperative medication to the start of induction of anesthesia. There were no statistically significant differences in the incidence of postoperative nausea and vomiting between groups K and T (Table 2).

The separation anxiety score and emergence agitation score did not differ significantly between the two groups (Table 3).

4. Discussion

In this study, we compared the effects of intravenous ketamine vs thiopental on satisfactory sedation upon separation from their parents and postoperative emergence agitation in children undergoing tonsillectomy with an

adenoidectomy and found that intravenous premedication with 0.1 mg/kg of ketamine and 3.0 mg/kg of thiopental in the preoperative holding area were equally effective in decreasing anxiety upon separation from parents. However, the administration of ketamine was associated with delayed emergence from anesthesia.

Anxiety in children undergoing surgery is characterized by subjective feelings of tension, apprehension, nervousness, and worry that may be expressed in various forms [1]. The moment of separation of the child from their parents while entering the operating room can be particularly difficult. Some children will explicitly verbalize their fears, while others will exhibit behaviors indicating distress, such as crying, screaming, nonverbal resistance and negative verbalizations [7]. Postoperative maladaptive behaviors, such as new onset enuresis, feeing difficulties, apathy and withdrawal, and sleep disturbances, may also result from anxiety before surgery. In fact, studies have indicated that up to 60 % of all children undergoing surgery may present with negative behavioral changes at 2 weeks postoperatively [1, 8]. Variables such as age, temperament, and anxiety of the child and parents in the preoperative holding area have been identified as predictors for these behavioral changes [1]. A previous study has demonstrated that practicing clinicians can predict the development of adverse postoperative phenomena, such as emergence delirium and postoperative behavioral changes, based on levels of preoperative anxiety [9, 10]. It has been suggested that high levels of preoperative anxiety, absence of analgesic block and presence of moderate and intense postoperative pain constituted risk factors for immediate postoperative anxiety in children [11].

The human response to surgical stress is characterized by a series of hormonal, immunological, and metabolic changes that together constitute the global surgical stress response [12, 13]. Children are particularly vulnerable to the global surgical stress response because of limited energy reserves, larger brain masses, and obligatory glucose requirements [14]. Acute psychological stress, such as preoperative anxiety, is associated with immediate stress hormone release. Various pharmacological and non-pharmacological techniques have been used to alleviate this situation. Most pharmacological methods are aimed at reducing anxiety and improving cooperation. Some children show good responses after watching a cartoon [15], playing video games [16], Clown doctors [17], low sensory stimulation [18], and music therapy [19]. A variety of drugs including benzodiazepines, barbiturates, opioids and ketamine have been used for premedication in children. The majority of children in the US are premedicated via the oral route, followed by nasal route, the IM route, and the rectal route [20]. However, most of the children in Korea are used to access intravenous route in the ward. Thus after arriving at the operating room, it was easily possible to administer the drugs through the intravenous route.

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, can induce a sedative state characterized by profound analgesia, amnesia, immobilization and dissociation from the environment. Advantages of ketamine include preservation of the upper-airway muscular tone and protective airway reflexes [21]. Disadvantages of ketamine as compared with other premedicants are increased salivary and bronchial secretions, which can lead to laryngospasm. Many authors suggested that salivation increases after ketamine administration [22]. Salivation could have been a problem for the surgeons during the procedure. However, salivation was prevented by atropine. Ketamine can also cause muscle rigidity and nystagmus in children, which can alarm the parents if they are not informed about this characteristic. Although unpleasant hallucinations and dreams during the recovery period have substantially limited the use of ketamine in adults, such dysphoric emergence reactions are rarely noted in children [23]. Intravenous administration of sedatives should be well-tolerated, and they should have a very short time for onset of anxiolysis.

Barbiturates control multiple vital functions including consciousness. Deep barbiturate sedation often leads to upper airway obstruction, and apnea usually occurs following an induction dose [24]. Thiopental is a commonly used barbiturate for the induction of anesthesia. Intravenously administered thiopental (3 mg/kg) has a rapid onset of action. In a preliminary study, 5 mg/kg of thiopental as a premedication had a risk of inducing respiratory depression. Therefore, we decided to use 3.0 mg/kg of thiopental for premedication. It was found that the administration of ketamine or thiopental was uneventful, cardiovascularly stable and was not associated with signs of airway irritation. In our study, anxiolysis was very successful. The administration of thiopental used to induce anesthesia is not necessary to administer other additional drugs.

Tonsillectomy with or without adenoidectomy is one of the most common outpatients surgical procedure in the pediatric population [25]. Major postoperative issues included pain, airway obstruction, and hypoventilation. It is known that patients undergoing head and neck procedures may have an increased incidence of emergence agitation [26]. The use of sevoflurane is a well-established practice in pediatric anesthesia. However, emergence agitation is a common post-anesthetic problem when using sevoflurane. The etiology of emergence agitation remains unknown. Many factors related to anesthesia, surgery, the patient, and adjunct medications have been suggested to play a potential role in the development of emergence agitation [27]. There are many conflicting reports which suggested that emergence agitation in patients varied between 5 and 100% [28]. Kwak HJ et al. [29] showed that intravenous injection of ketamine 1.0 mg/kg, after the induction of anesthesia in young children undergoing tonsillectomy with sevoflurane decreased the incidence of emergence agitation without a delay in recovery. However, in our study, there were no significant differences in the incidence of emergence agitation between the ketamine and thiopental group. It

could be considered that this was due to the routine use of fentanyl for pain control and the administration of ketamine or thiopental as a premedication.

The etiology of postoperative vomiting is multifactorial. Theoretically, patients undergoing tonsillectomy with adenoidectomy may be at an increased risk of bleeding because of vomiting. The reported incidence of vomiting after tonsillectomy in children is as high as 57% [30]. In our study, the incidence of postoperative nausea and vomiting was 23.8% in the ketamine group and 16.7% in the thiopental group. The incidence of postoperative nausea and vomiting in our study was lower than in the previous study because of observation of postoperative nausea and vomiting in the recovery room only. It could be considered that further research is needed to assess the effect of ketamine on postoperative nausea and vomiting.

5. Conclusions

This study is to compare the effect of injection intravenous ketamine or thiopental as premedication in preoperative holding area. Although recovery was slower in ketamine group, intravenous ketamine or thiopental in preoperative holding area is equally effective decreasing anxiety upon separation from parents. And it may not affect incidence of emergence agitation. The administration of thiopental used to induce anesthesia appears to be a better choice for preanesthetic medication with careful monitoring in children undergoing tonsillectomy with an adenoidectomy.

Table 1. *Demographic Data.*

	Group K (n = 42)	Group T (n = 42)
Age (years)	5.1 ± 2.0	4.7 ± 1.9
Sex (M/F)	16/26	18/24
Height (cm)	112.6 ± 13.2	110.9 ± 14.4
Weight (kg)	21.5 ± 6.4	21.7 ± 8.2
Duration of surgery (min)	43.8 ± 11.7	45.3 ± 9.3
Duration of anesthesia (min)	70.3 ± 12.8	70.6 ± 11.4

Values are expressed as mean ± SD or number of patients. There were no significant differences between the groups. Group K: administration of ketamine 1.0 mg/kg intravenously. Group T: administration of thiopental sodium 3.0 mg/kg intravenously in the preoperative holding area.

No significant differences were noted between the groups.

Table 2. *Recovery Parameters, and Postoperative Nausea and Vomiting.*

	Group K (n = 42)	Group T (n = 42)
Time to eye opening with verbal stimuli (min)	12.3 ± 3.4	9.7 ± 2.6*
Extubation time (min)	12.7 ± 3.1	10.0 ± 2.7*
Recovery room stay duration (min)	50.5 ± 6.8	53.8 ± 5.5
PONV scale (1/2/3/4)	32/3/6/1	35/1/6/0
Incidence of ondansetron injection	5 (11.9%)	3 (7.1%)

Values are expressed as mean ± SD or number of patients. PONV: postoperative nausea and vomiting. *P < 0.05 compared with group T. Group K: administration of ketamine 1.0 mg/kg intravenously. Group T: administration of thiopental sodium 3.0 mg/kg intravenously in the preoperative holding area.

Table 3. *Separation Anxiety Score and Emergence Agitation Score.*

	Group K (n = 42)	Group T (n = 42)
Separation anxiety score (1/2/3/4)	7/27/8/0	12/21/9/0
Emergence agitation score(1/2/3/4)	2/15/19/6	3/10/24/5

Values are expressed as number of patients. Group K: administration of ketamine 1.0 mg/kg intravenously. Group T: administration of thiopental sodium 3.0 mg/kg intravenously in the preoperative holding area.

No significant differences were noted between the groups.

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