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Research Article

Effect of oral dextromethorphan versus oral ketamine on sevoflurane related emergence agitation in children undergoing adenotonsillectomy

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KEYWORDS

Dextromethorphan;
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Abstract *Background:* Emergence agitation is a popular phenomenon after sevoflurane anesthesia. Our aim was to study the efficacy of oral dextromethorphan compared to oral ketamine on sevoflurane related agitation.

Methods: In a prospective, randomized, double- blinded study 120, ASA I, aged 4–10 years old children undergoing adenotonsillectomy were randomly divided into three groups to receive oral dextromethorphan 1 mg/kg (Group D, $n = 39$), oral ketamine 5 mg/kg (Group K, $n = 39$) or placebo(Group C, $n = 38$) as premedication 1 h before surgery. Standard general anesthesia was induced and maintained with sevoflurane in N_2O/O_2. The following were recorded by a blinded anesthetist; Child separation and cooperation at induction, duration of operation, duration of anesthesia, duration of extubation, duration of emergence, state of emergence on admission to PACU using emergence agitation scale, number of patients required postoperative fentanyl to control agitation, duration of discharge from PACU, vital signs (heart rate, blood pressure, and Spo_2) in PACU, and side effects (Nausea, vomiting, respiratory depression, and hallucination).

Results: The agitated patients that required fentanyl treatment were statistically significant low in groups D and K compared to group C ($p < 0.05$). Child separation and child cooperation at induction from parents was successful in all children in group K with statistical significant

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difference compared to other groups ($p < 0.05$).There were increases in duration of anesthesia, extubation, and emergence in group K compared to other groups without increase in the duration of stay in PACU.

Conclusion: Oral premedication with either dextromethorphan 1 mg/kg or ketamine 5 mg/kg were comparable in reducing significantly the incidence of postoperative sevoflurane related emergence agitation in comparison to placebo treated group without reported side effects in children undergoing adenotonsillectomy.

1. Introduction

Sevoflurane is a popular inhalational anesthetic agent used for induction and maintenance of anesthesia in pediatric patients. Because of its low blood solubility, it allows rapid induction and emergence from general anesthesia. However, when it is used as sole anesthetic agent, it is associated with a high incidence of emergence agitation (EA) that may be harmful to patients [1]. The exact etiology of EA is unknown, however; many explanations have been postulated including rapid removal of residual anesthetics, lack of adaptation of young children to the environment after awakening, anxiety from separation from their parents, increased pain sensation, and sympathetic hyperactivation [2].

Many authors used many drugs in attempts to reduce the incidence of EA including propofol [3], narcotics [4], alpha 2–agonists such as clonidine [5] or dexmedetomidine [6,7].

Ketamine, a competitive N-methyl D-aspartate (NMDA) receptor antagonist, has been reported in many studies to be effective in reducing the incidence of EA when administrated orally [8] or intravenously [2,9].

Dextromethorphan, the D-isomer of the codeine analog levorphanol, is another non competitive NMDA receptor antagonist which has been used for a long period as a central cough suppressant and analgesic adjuvant. The cough suppressant effect and the analgesic effect were attributed to its codeine analog structure and its NMDA receptor antagonistic action respectively [10]. It is metabolised in the liver to active metabolite, dextrorphan, which is responsible for its side effects through acting on phencyclidine receptors [11].

The aim of this study was to study the hypothesis that oral preoperative dextromethorphan can reduce the incidence of sevoflurane related emergence agitation in children, so we compared between oral dextromethorphan and oral ketamine when given one hour before surgery in a controlled double blind study on the incidence of emergency agitation in children undergoing adenotonsillectomy procedures.

2. Methods

After approval of the ethical committee in Dar Alshifa hospital (State of Kuwait), a written informed consent obtained from the parents of 120 children ASA physical status I aged 4–10 years old, undergoing adenotonsillectomy surgeries under general anesthesia during the period from September 2011 to March 2012. Children had history of cardiovascular, pulmonary or neurologic diseases, chronic cough, bronchial asthma, coagulation defects, an allergy to the studied drugs or recent upper respiratory tract infection within the previous 2 weeks, were excluded from this study.

On the morning of operation, the children were randomly divided using closed envelope technique for randomization to one of three groups according to the premedication drugs:

Group C (control) ($n = 40$) received oral water for injection.
Group D ($n = 40$) received oral dextromethorphan 1 mg/kg (Dextrokuf; Kuwait Saudi Pharmaceutical industries Co. 3 mg/ml).
Group K ($n = 40$) received oral ketamine 5 mg/kg (Ketam, Hikma pharmaceutical, Jordan, 50 mg/ml).

The premedication were mixed with apple juice prepared in 5 ml syringes by the nurses of the ward according to the instruction written in the sealed envelop and were given by the parents 60 min before the surgery. Both the anesthesiologists and anesthesia technicians of operating theatre were unaware of the used premedication except in emergency situation in order to ensure the double blind nature of the study.

Anesthesia technician assigned to the case received the child from parents and the observer recorded the separation using a separation score [12] (1 = Excellent: happily separated, 2 = Good: separated without crying, 3 = Fair: separated with crying, 4 = Poor: need for restraint) where 1 or 2 considered successful and 3 or 4 considered unsuccessful. Parents were allowed to attend the induction if separation was unsuccessful.

Children were fasting 4–6 h before surgery. In the operating room the ECG, pulse oximeter and noninvasive arterial blood pressure monitor were attached and the anesthesia was induced in all patients with sevoflurane 8 vol% in 50/50% O_2/N_2O (6 L/min) via face mask and the observer recorded cooperation of the children during induction using cooperation score at induction [12] (1 = Cooperative, 2 = Mildly resistant, 3 = Resistant to placement of face mask). After loss of consciousness, a peripheral venous catheter (22G or 24G) was inserted and dextrose 5% in 0.45% NaCl was infused at rate of 4 ml kg^{-1} h^{-1}. Orotracheal intubation was done using a suitable size, lubricated, and cuffed preformed tube. Anesthesia was maintained with sevoflurane 3–4 vol% in 50/50% O_2/N_2O. Spo_2, end-tidal carbon dioxide, heart rate, and noninvasive arterial blood pressure were monitored continuously. Immediately after intubation, a suppository of paracetamol (Adol, Julphar Pharmaceutical Industries, UAE) 15 mg/kg was given. Spontaneous breathing was allowed and assisted ventilation had been performed if $ETco_2$ had exceeded 45 mm Hg. No sedative, muscle relaxant or narcotic was given during the procedure. The same surgeon performed all the operations to ensure the same duration of operation which recorded from application of the mouth gage till removal of the mouth gage (before removal of the mouth gag, the surgeon

Table 1 Demographic data and duration of operation.

	Group C (n = 38)	Group D (n = 39)	Group K (n = 39)
Age (years)	6.5 (1.7)	6.6 (1.5)	6.4 (1.5)
Sex (male/female)	23/15	21/18	24/15
Weight (kg)	23.3 (3.5)	22.8 (3.3)	23.1 (3.4)
Duration of operation (min)	40.2 (2.6)	40.6 (2.6)	41.2 (2.4)

Group C: control group. Group D: dexromethorphan group. Group K: ketamine group. Values are presented as mean (SD) or number,
No significant difference among the studied groups.

Table 2 Child separation from parents and cooperation at induction.

	Group C (n = 38)	Group D (n = 39)	Group K (n = 39)
Successful separation	3 (8)	3 (8)	25 (64)*,**
Cooperation Score at induction	2 (2-3)	2 (2-3)	1 (1–2)

Group C: control group. Group D: dexromethorphan group. Group K: ketamine group. Values are presented as number (percentage) or median (range),
* Significant difference ($p < 0.05$) Compared to group C.
** Significant difference ($p < 0.05$) Compared to group D.

applied a gauze soaked with lidocaine 2% in the tonsillar bed). At the end of surgery, sevoflurane and N_2O were discontinued, and the patients were extubated after return of the gag reflex. After extubation the patients were given O_2 100% via face mask until eye opening on verbal command.

The patients were shifted to post anesthesia care unit (PACU) for observation and monitoring until a score 9 or more on Modified Aldrete postanesthesia score [13] were reached for discharge.

The following variables were evaluated during the study.

- Demographic data.
- Child separation from parents and cooperation at induction.
- The duration of operation (the time between application and removal of the mouth gag).
- The duration of anesthesia (the time from induction of anesthesia to extubation).
- The duration of extubation (the time from discontinuation of the anesthetic to extubation).
- The duration of emergence (The time from the discontinuation of anesthesia till the time of eye opening on verbal command).
- State of emergence on admission to PACU using emergence agitation scale [12]: 1 = Obtunded with no response to stimuli; 2 = Asleep, but responsive to movement and stimuli; 3 = Awake and appropriately responsive; and 4 = Crying and difficult to console; 5 = Wild thrashing behavior that requires restraint. For the study, the score of 4 or more was considered agitation and required treatment with intravenous increments of fentanyl 1 μg/kg with interval of 10 min between doses with monitoring for any signs of respiratory depression.
- The number of patients required postoperative fentanyl.
- The duration of discharge from PACU (from arrival to the PACU until discharge).
- Vital signs (heart rate, blood pressure, and Spo_2) were monitored in PACU on admission and every 10 min until discharge.
- Side effects:
- Nausea and vomiting using a 4-degree scale [4]: 0 = absence of nausea and vomiting; 1 = nausea only; 2 = single emetic episode; 3 = multiple emetic episodes. (Treated with Ondansetron 0.15 mg/kg which can be repeated up to total dose 4 mg.)
- Respiratory depression detected by O_2 desaturation.
- Hallucination.

3. Statistical analysis

We calculated the sample size of 30 patients in each group depending on the results from previous studies assuming a reduction in the incidence of agitation from 60% to 30% with the α-error level was fixed at 0.05 and the power was set at 90%. We expected some exclusion, so we increased the number of the sample size to 40 patients per group.

Data values were presented as means (SD), median (range) or number (percentages). Numerical data were analyzed by using One-way, independent-measures ANOVA. Nonparametric data were analyzed by using the Kruskal-Wallis test. A value of $p < 0.05$ was considered significant. All statistical analysis was performed using (Microsoft office Excel).

4. Results

The demographic data and operation time were presented in (Table 1). Two patients in group C, one patient in group D, and one patient in group K were excluded from the study due to bleeding at the surgical region after extubation. The three groups were similar regarding age, sex, weight, and operation time.

Child separation from parents was successful in all children in group K with statistical significant difference compared to groups C and D ($p < 0.05$) without statistical difference between groups C and D being (100%, 8%, and 5% in group K, C, and D respectively); Also child cooperation at induction

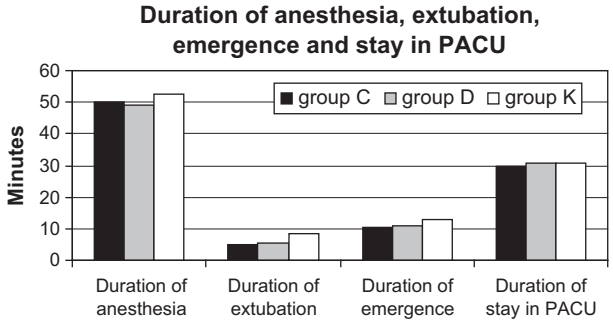

Figure 1 Durations of anesthesia, extubation, emergence, and stay in PACU. Group C: control group. Group D: dexromethorphan group. Group K: ketamine group.

Table 3 Incidence and severity of agitation and Patients received fentanyl.

Variables	Group C (n = 38)	Group D (n = 39)	Group K (n = 39)
Grades of agitation			
Grade 1	0 (0)	0 (0)	0 (0)
Grade 2	0 (0)	12(31)*	15 (38)*
Grade 3	8 (21)	20(51)*	20 (51)*
Grade 4	20 (52)	4 (10)*	3 (8)*
Grade 5	10 (26)	3(8)*	1 (2)*
Agitated patients received fentanyl(n)	30 (79)	7 (18)	4 (10)

Group C: control group. Group D: dexromethorphan group. Group K: ketamine group. Values are presented as number (percentage),
* Significant difference ($p < 0.05$) Compared to group C.

was better in group K compared to other groups with no significant difference between groups C and D (Table 2).

There were increases in duration of anesthesia, duration of extubation, and duration of emergence in group K compared to other groups with no difference between groups C and D; however the duration of stay in PACU were similar in the three groups (Fig. 1).

The agitated patients (grade 4 and 5) that required fentanyl treatment were statistically significant low in groups D and K compared to group C ($p < 0.05$) with no significant difference between groups D and K. Number of patients of grade 2 and 3 were statistically significant more in groups D and K compared to group C ($p < 0.05$) with no significant difference between groups D and K (Table 3).

There were no significant difference among the studied groups regarding the heart rate, mean blood pressure, and Spo2 recorded in PACU on admission and every 10 min until discharge (Figs. 2–4).

There was no significant difference among the studied groups regarding the incidence of nausea without occurrence of vomiting, respiratory depression or hallucination in any patient of the studied groups (Table 4).

5. Discussion

Sevoflurane-related emergence agitation (EA) is still considered a significant post-anesthetic problem with children's recovery. In spite of its spontaneous resolution, its etiology remains unclear. Inadequate analgesia may be the cause of agitation [14] especially after short surgical procedures.

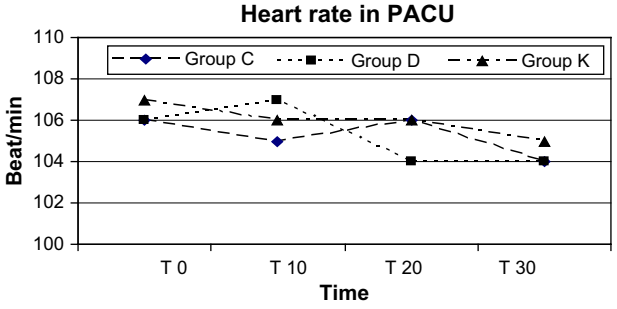

Figure 2 Heart rate in PACU at admission (T0), 10 (T10), 20 (T20), and 30 (T30) minutes. Group C: control group. Group D: dexromethorphan group. Group K: ketamine group.

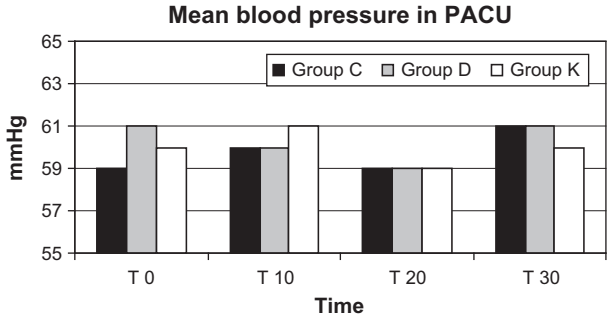

Figure 3 Mean blood pressure in PACU at admission (T0), 10 (T10), 20 (T20), and 30 (T30) minutes. Group C: control group. Group D: dexromethorphan group. Group K: ketamine group.

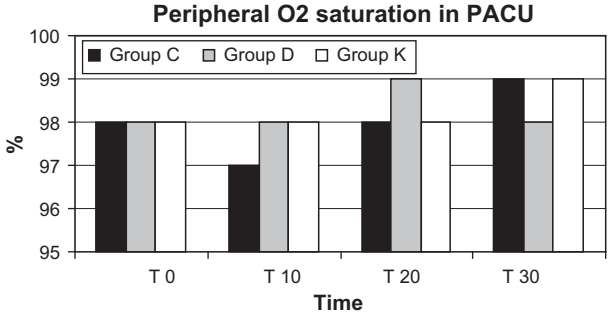

Figure 4 Peripheral O2 saturation in PACU at admission (T0), 10 (T10), 20 (T20), and 30 (T30) minutes. Group C: control group. Group D: dexromethorphan group. Group K: ketamine.

In our study, to optimize pain management we used a suppository of paracetamol 15 mg/kg immediately after intubation and the surgeon applied gauze soaked with lidocaine 2% in the tonsillar bed at the end of operation.

It has been suggested that rapid recovery after the use of the sevoflurane, may initiate EA. However, this suggestion was not approved because of rapid smooth recovery after propofol anesthesia with low incidence of EA compared to sevoflurane [15]. So, It has been suggested that sevoflurane-related EA is a sevoflurane intrinsic character, particularly in younger children [16].

Table 4 Incidence of side effects in PACU.

	Group C (n = 38)	Group D (n = 39)	Group K (n = 39)
Nausea	3 (7)	2 (5)	3 (8)
Vomiting	0 (0)	0 (0)	0 (0)
Respiratory depression	0 (0)	0 (0)	0 (0)
Hallucination	0 (0)	0 (0)	0 (0)

Group C: control group. Group D: dexromethorphan group. Group K: ketamine group. Values are presented as number (percentage).
No significant difference among the studied groups.

Dextromethorphan was used in a dose of 1 mg/kg after reviewing the safe pediatric doses in previous reports [17,18] that used dextromethorphan orally in a dose of 1 mg/kg in children without reported side effects.

Due to the lack of reports about dextromethorphan use in prevention of sevoflurane induced EA in previous studies, the results of studies including other NMDA receptor antagonists were compared. Ketamine has been found to be effective in preventing EA in children in many studies; Khattab and El-Seify who used ketamine 2 mg/kg plus midazolam 0.5 mg/kg as oral premedication in dental surgery in preschool children [19]. Kawarguchi et al. used ketamine 1 mg/kg i.v. after sevoflurane induction of anesthesia in strabismus surgery in children [20]. Dalens et al. used ketamine 0.25 mg/kg i.v. just before sevoflurane discontinuation in children undergoing cerebral MRI [21]. Lee et al. used ketamine 0.25 mg/kg or 0.5 mg/kg intravenous 10 min before the end of surgery in children undergoing tonsillectomy and adenoidectomy [2].

In our result we found that the use of oral dextromethorphan as a premedication reduced the incidence of EA compared to control group (from 79% to 18%). Also, we found that both oral dextromethorphan and oral ketamine were effective in reducing the incidence of EA. The mechanism by which the dextromethorphan reduced the incidence of EA may be the same like ketamine which inhibits the CNS effect in ether-linked inhalation anesthetics and stimulates the release of melatonin which has beneficial effects in reducing emergence agitation following sevoflurane anesthesia in children [22].

In this study, the child separation from parents was better with ketamine (64%) than dextromethorphan (8%) and placebo (8%). Also, the face mask application was easy with ketamine than dextromethorphan and placebo. This is inconsistent with the result of Alderson and Lerman [23] who found successful separation in 65% of children and also, 65% of children were calm or apprehensive with face mask application with oral ketamine 5 mg/kg and the study of Turhanoglu and colleagues [24] found 55% successful children separation and easy face mask application with oral ketamine 6 mg/kg.

In this study, both dextromethorphan and ketamine use was not associated with significant side effects and this is in agreement with the previous studies [25,17]. This can be explained that oral administration of dextromethorphan avoids the tachycardia and hypotension side effects of intravenous administration because of only 10% bioavailability after oral dose [11], also oral administrated ketamine has only 16% bioavailability because of high hepatic first pass effect with a metabolite norketamine which causes sedation and analgesia and devoid of hallucination associated with the parenteral route [26].

We concluded that oral premedication with either dextromethorphan 1 mg/kg or ketamine 5 mg/kg were comparable in reducing significantly the incidence of postoperative sevoflurane related emergence agitation in comparison to placebo treated group without reported side effects in children undergoing adenotonsillectomy, and ketamine premedication improved child separation from parents and face mask application at induction with slight prolongation of extubation, emergence, and anesthesia durations when compared to both dextromethorphan and placebo treated groups.

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