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ORIGINAL ARTICLE

The effect of alfentanil versus ketamine on the intubation condition and hemodynamics with low-dose rocuronium in children

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Abstract
Purpose We investigated the effect of alfentanil and ketamine on the intubation condition and hemodynamic parameters during propofol anesthesia with low-dose rocuronium in children.
Methods Fifty-four children, aged 3–9 years undergoing tonsillectomy, were randomly allocated to receive either alfentanil 20 μg/kg (alfentanil group, $n = 27$) or ketamine 0.5 mg/kg (ketamine group, $n = 27$) 1 min before anesthesia induction. Anesthesia was induced with propofol 2.5 mg/kg and rocuronium 0.3 mg/kg and maintained with propofol infusion (6 mg/kg/h). The neuromuscular relaxation was monitored, and intubation conditions, hemodynamic changes, and recovery time were assessed.
Results All patients were successfully intubated and there were no significant differences in the intubation conditions between alfentanil and ketamine groups. At the time of tracheal intubation, the median [inter-quartile range] twitch height was similar between two groups (37 [4–48] % in the alfentanil group vs. 29 [4–43.5] % in the ketamine group, $p = 0.326$).
Conclusions This study showed that both ketamine 0.5 mg/kg and alfentanil 20 μg/kg provided adequate intubation condition during propofol induction with low-dose rocuronium in children. The mean arterial pressure and heart rate were higher in the ketamine group after propofol injection but they remained within the normal limit in both groups throughout the study period.

Keywords Alfentanil · Children · Ketamine · Low-dose rocuronium · Propofol

Introduction

Adeno-tonsillectomy is a common, elective, short surgical procedure that requires general anesthesia in children. For short surgeries, minimum dose of rocuronium to produce an acceptable intubation condition is preferred because a higher dose of rocuronium prolongs the time of muscular recovery without further improving the intubation condition [1]. However, low-dose rocuronium delays the onset time of neuromuscular blockade [2] and may cause an inadequate intubation condition that leads to coughing, bucking, and laryngospasm, which can be fatal in small children with low functional residual capacity.

For pediatric patients, sevoflurane is widely used for induction of anesthesia. However, since sevoflurane augments the effect of rocuronium, which makes the duration unpredictable [3], alfentanil and ketamine has been used to facilitate the tracheal intubation without neuromuscular blockade during propofol induction [4, 5]. Propofol has hemodynamic depressant effects through direct suppression of peripheral vascular resistance and myocardial contractility [6] and alfentanil has been shown to potentiate the hemodynamic depressant effects of propofol in children [7, 8]. Ketamine has the properties of sympathetic activation, which can improve hemodynamic stability [5, 6] and accelerate the onset time of low-dose rocuronium when administered with propofol during anesthesia induction [9, 10]. Therefore, we

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hypothesized that compared to alfentanil, ketamine would provide better intubation conditions and maintain higher mean arterial pressure (MAP) during propofol induction with low-dose rocuronium. Accordingly, the aim of this study was to investigate the effect of alfentanil and ketamine on the intubation condition and hemodynamic parameters during propofol anesthesia with low-dose rocuronium 0.3 mg/kg in children undergoing adeno-tonsillectomy.

Methods

After obtaining institutional review board approval from the university hospital and written informed consent from the parents, 54 children, ASA physical status I, aged 3–9 years and undergoing adeno-tonsillectomy were studied. Patients with known allergy to ketamine and the opioids, the symptoms of upper respiratory infection, a neuromuscular disorder, an anticipated difficult airway, and crying children on arrival in the operating theatre were excluded from the study. Children were randomly allocated to receive either alfentanil 20 μg/kg (alfentanil group, $n = 27$) or ketamine 0.5 mg/kg (ketamine group, $n = 27$) before anesthesia induction using a computer-generated randomization list generated by a statistician in a sealed envelope (Fig. 1). An independent researcher prepared the study solution consisting of a 5-ml mixture of alfentanil 20 μg/kg and normal saline in the alfentanil group and ketamine 0.5 mg/kg and normal saline in the ketamine group.

Premedication with i.m. glycopyrrolate 4 μg/kg was administered 1 h before anesthesia induction. Before arrival in the operating room, a 24-gauge cannula was inserted in the dorsum of the hand. On arrival in the operating room, patients were monitored with standard anesthetic monitors including electrocardiogram, pulse oximeter, and non-invasive arterial pressure. After pre-oxygenation, the study drug was administered according to their treatment group. After 1 min, a bolus dose of propofol 2.5 mg/kg was administered over 20 s. Mask ventilation was initiated with 100 % oxygen after the loss of eyelash reflex and rocuronium 0.3 mg/kg was administered. Propofol 6 mg/kg/h was infused immediately after the administration of rocuronium for maintenance of anesthesia.

The neuromuscular relaxation was monitored with a TOF-Watch© (Organon Teknika, Eppelheim, Germany) through a transducer attached to the volar surface of the thumb. The stimulation electrodes were placed over the ulnar nerve to give continuous supramaximal stimulation (0.1 Hz, single twitch mode), which started before the rocuronium injection. At 2 min after the rocuronium administration (the time of tracheal intubation), the twitch height was recorded.

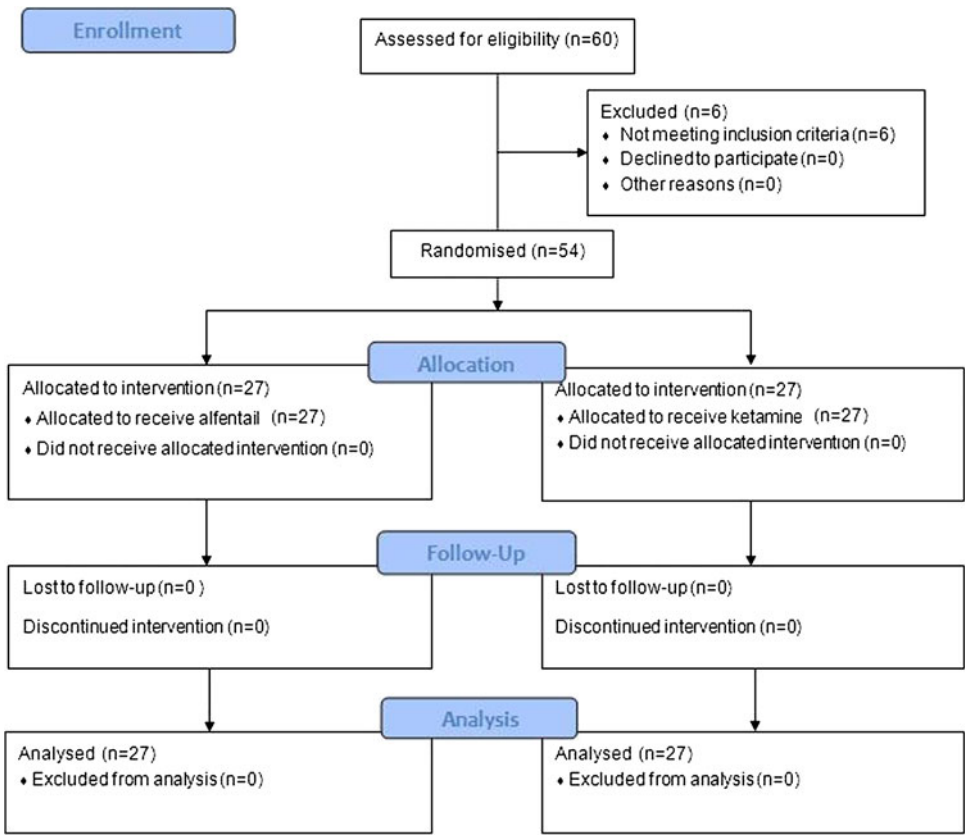

Fig. 1 Flow CONSORT diagram

Two minutes after the administration of rocuronium, laryngoscopy was attempted and intubation condition was assessed by the same anesthesiologist blinded to the study group. We used the scoring system described by Viby-Mogensen et al. [11]. The criteria of intubation condition included five variables, which are jaw relaxation, vocal cord position, vocal cord movement, airway reaction (coughing), and movement of the limbs. Each variable was rated as excellent, good, or poor. "Excellent" intubation condition was defined when all criteria are excellent and "good" intubation condition defined when all criteria are either excellent or good. If any variable was rated as poor due to the patients' strong movement, inadequate jaw relaxation, closed vocal cords, or sustained coughing, then additional rocuronium 0.3 mg/kg was administered.

Hemodynamic variables including heart rate (HR) and MAP were measured and recorded at the following selected time points: T0, before anesthesia induction; T1, immediately after administration of the study drug; T2, immediately after administration of propofol; T3, immediately before tracheal intubation; T4, 1 min after tracheal intubation. The clinically significant hypotension and bradycardia were defined as HR <55 beats/min and MAP <55 mmHg, respectively. They were treated with atropine or ephedrine where appropriate.

Sample size calculated based on a previous study [12]. To detect a 40 % difference in the incidence of excellent intubation condition during propofol induction at a significant level of 5 % and a probability power of 80 %, this study required at least 23 patients per group. The sample size was increased to 27 patients per group assuming 15 % dropout rate. Values are expressed as mean ± SD or median [interquartile range] or number of patients. The distribution of all measure and calculated data are tested by Kolmogorov–Smirnov tests. The patients' characteristics and induction profiles were compared using an unpaired *t* test or Chi-square test. The changes in the hemodynamic data were compared by repeated measures ANOVA with post hoc Bonferroni's test. Significance was defined as $p < 0.05$.

Results

A total of 54 patients completed the study. There were no significant differences in age, gender, and weight between the two groups, and in terms of the propofol and rocuronium injection pain, there were no significant differences between the groups (Table 1).

Intubation conditions are shown in Table 2. All patients were successfully intubated and no patient showed poor intubation condition (failed intubation) in this study. There were no significant differences in the intubation conditions between the groups. Excellent intubation condition was present in 16/27 (59 %) and 13/27 (48 %), and good intubation condition in 11/27 (41 %) and 14/27 (52 %) children in the alfentanil and ketamine groups, respectively. At 2 min after the rocuronium administration (the time of tracheal intubation), the median [inter-quartile range] twitch height was similar between two groups (37 [4–48] % in the alfentanil group vs. 29 [4–43.5] % in the ketamine group, $p = 0.326$).

Hemodynamic data are shown in Fig. 2. MAP and HR were significantly higher at T2 in the ketamine group compared with the alfentanil group ($p = 0.02$ and $p = 0.011$, respectively). In the ketamine group, MAP was decreased at T3 but increased at T4 compared with baseline values at T0. In the alfentanil group, MAP was decreased at T2 and T3 compared to the baseline value. The HR was increased at T2 compared to the baseline value in the ketamine group. There was no change in the HR in the alfentanil group.

Table 1 Patient characteristics and induction profiles

	Alfentanil group ($n = 27$)	Ketamine group ($n = 27$)
Age (years)	7.3 ± 1.4	6.9 ± 1.4
Gender (male/female)	15/12	16/11
Weight (kg)	32.8 ± 23.0	28.8 ± 21.7
Cough during induction	2	0
Injection pain		
Propofol	7	3
Rocuronium	6	13

Values are mean ± SD or number of patients. There are no significant differences between two groups

Table 2 Conditions during tracheal intubation

	Alfentanil group ($n = 27$)	Ketamine group ($n = 27$)
General condition		
Excellent/good/poor	16/11/0	13/14/0
Jaw relaxation		
Easy/fair/difficult	24/3/0	21/6/0
Vocal cord position		
Abducted/intermediate/closed	25/2/0	23/4/0
Vocal cord movement		
None/moving/closing	25/2/0	22/5/0
Coughing		
None/diaphragm/sustained	16/11/0	14/13/0
Movement of the limbs		
None/slight/vigorous	16/11/0	14/13/0

Values are number of patients. There are no significant differences between two groups

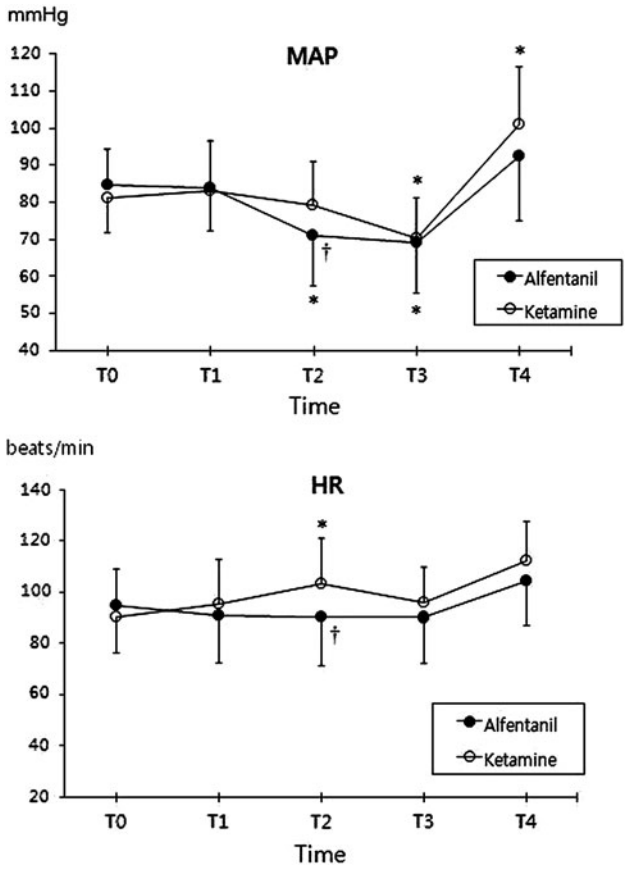

Fig. 2 Changes in mean arterial pressure (*MAP*) and heart rate (*HR*). *T0* before anesthesia induction, *T1* immediately after administration of the study drug, *T2* immediately after administration of propofol, *T3* immediately before tracheal intubation, *T4* 1 min after tracheal intubation. *$p < 0.05$ versus T0 within the group; †$p < 0.05$ versus ketamine group

No patents had episodes of tachy- or brady-arrhythmia or hypotension requiring treatment during the study. No patents suffered from desaturation, truncal rigidity, or laryngospasm throughout the study period.

Discussion

This study demonstrated that both ketamine 0.5 mg/kg and alfentanil 20 μg/kg provided adequate intubation condition during propofol induction with low-dose rocuronium 0.3 mg/kg in children undergoing adeno-tonsillectomy. The MAP and HR were higher in the ketamine group after propofol injection but they remained within normal limit in both groups throughout the study period.

Several adjuvant drugs have been studied for tracheal intubation without neuromuscular blocking agent in children [4, 5, 7] because single-dose rocuronium 0.6 mg/kg for tracheal intubation may outlast brief pediatric procedures [13, 14]. However, since high-dose sedative agents may cause hemodynamic instability and delay the emergence from anesthesia, low-dose muscle relaxant has been studied with adjuvant drugs such as alfentanil and ketamine to hasten the onset time and provide better intubation condition [10, 12, 15].

Alfentanil has been used to facilitate tracheal intubation due to its ability to blunt laryngeal reflexes [12, 15, 16]. In this study, all children using alfentanil 20 μg/kg achieved clinically acceptable intubation conditions (excellent 59 % and good 41 %) at 2 min after the injection of rocuronium 0.3 mg/kg, without hemodynamic depression requiring the treatment. These results were similar to those of a previous report by Bartolek et al. [15] who showed that the addition of alfentanil 20 μg/kg during anesthesia induction with propofol 2.5 mg/kg and rocuronium 0.45 mg/kg provided clinical acceptable intubation condition in 95 % of children (excellent 80 % and good 15 %) without significant hemodynamic instability [15].

The onset of neuromuscular blocking agents is accelerated by the increase in cardiac output and muscle blood flow [17]. Previous studies reported that induction agents that maintain hemodynamic stability such as etomidate or ketamine were associated with faster onset times of rocuronium and improved the intubation conditions [18–20]. Co-administration of ketamine and rocuronium has been shown to facilitate tracheal intubation in adult patients [10, 20]. Topcuoglu et al. [10] reported that the combination of 0.5 mg/kg of ketamine and 2.5 mg/kg of propofol improved the intubation conditions at 60 s after the administration of 0.6 mg/kg of rocuronium through sympathomimetic effects, which may have accelerated distribution of rocuronium. In this study, we hypothesized that ketamine 0.5 mg/kg would provide better intubation condition with higher MAP through rapid distribution of rocuronium compared to alfentanil 20 μg/kg in children. However, there was no difference in intubation conditions between the two groups and the frequency of excellent intubation condition were comparable (59 % in the alfentanil group vs. 48 % in the ketamine group, $p = 0.586$). The twitch height of the adductor pollicis muscle was also similar in two groups at 2 min after rocuronium injection between the two groups. In addition, there were no differences in MAP and HR between the groups except at immediately after propofol injection (about 90 s after the administration of the study drugs). Although we were unable to show the differences in intubation conditions and neuromuscular monitoring between the groups, an additional study using a smaller dose of alfentanil such as 10 μg/kg may have shown the superiority of ketamine over alfentanil.

One of the limitations of this study is that we did not measure the cardiac output during anesthesia induction to confirm the hemodynamic effects of ketamine. However, it is ethically unacceptable to use invasive monitoring for

brief procedures that may benefit through the use of low-dose rocuronium in children. Another limitation is the lack of TOF data for the duration of rocuronium. If the duration of rocuronium was different, the adjustment of the dosage would have given a different result.

In conclusion, the addition of ketamine 0.5 mg/kg or alfentanil 20 μg/kg during anesthesia induction with propofol with low-dose rocuronium 0.3 mg/kg achieved clinically acceptable intubation conditions in all children.

Conflict of interest None declared.

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