Remifentanil-based total intravenous anesthesia for pediatric rigid bronchoscopy: comparison of adjuvant propofol and ketamine

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OBJECTIVE: Laryngoscopy and stimuli inside the trachea cause an intense sympatho-adrenal response. Remifentanil seems to be the optimal opioid for rigid bronchoscopy due to its potent and short-acting properties. The purpose of this study was to compare bolus propofol and ketamine as an adjuvant to remifentanil-based total intravenous anesthesia for pediatric rigid bronchoscopy.

MATERIALS AND METHODS: Forty children under 12 years of age who had been scheduled for a rigid bronchoscopy were included in this study. After midazolam premedication, a 1 μg/kg/min remifentanil infusion was started, and patients were randomly allocated to receive either propofol (Group P) or ketamine (Group K) as well as mivacurium for muscle relaxation. Anesthesia was maintained with a 1 μg/kg/min remifentanil infusion and bolus doses of propofol or ketamine. After the rigid bronchoscopy, 0.05 μg/kg/min of remifentanil was maintained until extubation. Hemodynamic parameters, emergence characteristics, and adverse events were evaluated.

RESULTS: The demographic variables were comparable between the two groups. The decrease in mean arterial pressure from baseline values to the lowest values during rigid bronchoscopy was greater in Group P ($p = 0.049$), while the reduction in the other parameters and the incidence of adverse events were comparable between the two groups. The need for assisted or controlled mask ventilation after extubation was higher in Group K.

CONCLUSION: Remifentanil-based total intravenous anesthesia with propofol or ketamine as an adjuvant drug along with controlled ventilation is a viable technique for pediatric rigid bronchoscopy. Ketamine does not provide a definite advantage over propofol with respect to hemodynamic stability during rigid bronchoscopy, while propofol seems more suitable during the recovery period.

KEYWORDS: Rigid Bronchoscopy; Pediatric Anesthesia; Remifentanil; Ketamine; Propofol.

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INTRODUCTION

Rigid bronchoscopy (RB) is the technique of choice for the removal of tracheobronchial foreign bodies (1) also a useful tool for other diagnostic or therapeutic purposes. Despite its advantages, RB is more stimulating than fiberoptic bronchoscopy and, therefore, requires general anesthesia. Laryngoscopy and stimuli inside the trachea cause an intense sympatho-adrenal response (2); therefore, it is reasonable to use high-dose opioids during RB because the noxious stimuli associated with RB have been shown to be qualitatively similar to those of laryngoscopy but are often greater and of longer duration (3). Remifentanil seems to be the optimal opioid for RB with because of its potent and ultra-short-acting properties. In addition, minimal analgesia is required after the procedure.

The favorable pharmacokinetic profile and quick metabolism of remifentanil and propofol make them agents of choice for total intravenous anesthesia (TIVA) (4,5). Both remifentanil and propofol can decrease blood pressure and heart rate, and this hemodynamic effect can be additive or synergistic with the combined use of both drugs (4,6).

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Ketamine has a minimal eaffect on ventilatory drive, exhibits bronchodilating properties (7), and has been used mostly for flexible bronchoscopy with spontaneous ventilation (8). In contrast to remifentanil and propofol, ketamine increases arterial blood pressure, heart rate, and cardiac output (7,9). There is limited data regarding remifentanil-based anesthesia for RB or data comparing ketamine and propofol during remifentanil infusion. In this study, we aimed to compare bolus infusions of propofol and ketamine as an adjuvant to remifentanil-based anesthesia for pediatric RB. The hemodynamic parameters, RB conditions, emergence characteristics, and adverse events were evaluated.

MATERIALS AND METHODS

After obtaining the approval of the Institutional Ethics Committee and obtaining informed consent from the parents, 40 consecutive children under 12 years of age who were scheduled to undergo RB for diagnostic (suspected foreign body aspiration, bronchoalveolar lavage) and/or therapeutic purposes (removal of foreign bodies and/or mucus plugs) were included. Patients were excluded if they had severe cardiovascular disease; cerebral, hepatic, or renal dysfunction; or neuromuscular disease. Children with predicted difficulty in laryngoscopy and intubation, those requiring prompt interventions for a life-threatening situation (acutely compromised airway with SpO_2 values below 70%), and patients scheduled for additional interventions or surgery subsequent to RB were also excluded.

The fasting time before anesthesia induction was at least six hours for solid foods and four hours for clear liquids. Before admission to the preoperative holding area, a local anesthetic cream was applied to the insertion site and intravenous (IV) catheterization was performed. Midazolam (0.05 mg/kg) was administered intravenously just before admission to the operating room. Pulse oximetry (SpO_2), electrocardiogram (ECG), and non-invasive blood pressure were monitored. Before induction, all children were pre-oxygenated and a 10 mg/kg/h crystalloid infusion was started. Children were randomly allocated to one of two groups using sealed envelopes. After a second dose of 0.05 mg/kg of IV midazolam, a 1 μg/kg/min remifentanil infusion (RI) was started. During the 1st minute of RI, 2-4 mg/kg of propofol (Group P) or 2-3 mg/kg of ketamine (Group K) was administered. To prevent propofol injection pain, propofol was included 1 mg/ml of lidocaine. When adequate mask ventilation was ensured, 0.15 mg/kg of mivacurium was administered for muscle relaxation, and RB was initiated during the 4th-5th minutes of RI. The depth of anesthesia was assessed clinically based on hemodynamic parameters (heart rate, blood pressure), movement, coughing, bucking, lacrimation, and sweating. Additional doses of propofol (0.5-1 mg/kg) or ketamine (0.25-0.5 mg/kg), with or without mivacurium (0.025-0.05 mg/kg, according to the bronchoscopy course), were administered if the anesthesia was considered inadequate. A 1 μg/kg/min remifentanil infusion was maintained throughout the procedure.

Patients were manually ventilated with a 'T' piece connected to the side arm of the rigid bronchoscope (Karl Storz; Tuttlingen, Germany). The fresh gas flow was adjusted to 6-10 l/min. In case of major air leakage, an oxygen flush valve was used for adequate filling of the reservoir bag and the airway pressure limit was adjusted to 20-30 cmH_2O.

After bronchoscopy, endotracheal intubation was performed and manually controlled or assisted ventilation with 4-8 cmH_2O positive end-expiratory pressure (PEEP and 50% oxygen in air was performed. Tracheal and oral secretions were suctioned as needed, and the patients were turned to the lateral decubitus position for recovery. After being placed in the recovery position, no further stimulation was allowed except gentle suctioning of oral secretions. For a smooth extubation, RI was decreased to 0.05 μg/kg/min and continued until just before extubation. When patients began to demonstrate emergence from anesthesia by displaying a regular respiratory pattern, facial grimacing, or purposeful movement, the trachea was extubated. In cases of breath-holding and arterial oxygen desaturation, assisted or controlled mask ventilation was performed. Pure oxygen was administered via the mask to maintain SpO_2 above 94%.

Noninvasive blood pressure was measured before induction as a baseline value, after induction (just before laryngoscopy), and in three-minute intervals during RB. Hypotension was defined as a systolic blood pressure lower than 60 mmHg for children under two years of age and 70 mmHg for children 2-12 years of age (10). Hypotension was treated with an increase in IV crystalloid infusion, and cases with two consecutive measures of hypotension were treated with ephedrine and a decrease in the remifentanil infusion. Bradycardia was defined as a heart rate slower than 80 beats/min for infants and 60 beats/min for older children (11) and was treated with atropine 0.01 mg/kg.

SpO_2 values below 90% were defined as hypoxemia. The severity of hypoxemia was graded as mild (SpO_2: 80-89%), moderate (SpO_2: 70-79%), or severe (SpO_2: <70%). Coughing or respiratory effort (diaphragm movement) and limb movement during laryngoscopy and RB were graded as mild (minor movement that does not affect surgical comfort), moderate (affects surgical comfort), or severe (the bronchoscope has to be removed to prevent complications) by the endoscopist. Postoperative severe restlessness and disorientation with purposeless activity were defined as emergence agitation. All adverse events were recorded by an independent observer.

The primary outcome of the study was the change in systolic arterial pressure during RB. A pilot study was performed with the technique used for Group P. A power analysis showed that a minimum sample size of 40 patients (20 in each group) was required to detect a 20% change in systolic arterial pressure at a power level of 90% with $p<0.05$. Categorical variables and hemodynamic parameters were analyzed using the Mann-Whitney U test and repeated-measures analysis of variance (ANOVA), respectively. A comparison of the incidence of the outcomes between the two groups was performed using a two-tailed Fisher's exact test. The results were considered to be statistically significance at $p<0.05$.

RESULTS

Patient and anesthesia characteristics are listed in Table 1. The age, weight, gender distribution, and duration of RB were comparable between the two groups. One patient in Group P developed respiratory distress and was excluded. It was not possible to introduce the rigid bronchoscope in

Table 1 - Patient and anesthesia characteristics.

	Group P	Group K
Age (years)	3.9 (±4)	3.3 (±3)
Weight (kg)	15.7 (±10)	14.9 (±6)
Gender (Male/Female)	12/8	13/7
Duration of RB (min)	13.9 (±6.7)	10.3 (±4)
Total midazolam administered (mg/kg)	0.09 (±0.02)	0.10 (±0.01)
Propofol induction dose (mg/kg)	2.87 (±0.52)	-
Total propofol administered (mg/kg)	4.75 (±1.94)	-
Total lidocaine administered (mg/kg)	0.47 (±0.19)	-
Ketamine induction dose (mg/kg)	-	2.30 (±0.39)
Total ketamine administered (mg/kg)	-	2.87 (±0.67)
Mivacurium induction dose (mg/kg)	0.16 (±0.04)	0.16 (±0.04)
Total mivacurium administered (mg/kg)	0.18 (±0.05)	0.18 (±0.04)
Additional mivacurium (*n*=)	6	8
Atropine administration (*n*=)	1	3
IV steroid administration (*n*=)	4	6

Values are expressed as the mean±SD or number of patients (*n*). RB: rigid bronchoscopy.

this patient; therefore, an optical telescope was used while manually controlled ventilation was performed successfully with a nasopharyngeal tube. The same consultant with four years of experience in pediatric anesthesia administered the anesthesia for all procedures. Six different endoscopists (four residents and two pediatric surgery consultants) performed the RB. RB was sometimes started by a non-experienced endoscopist (resident) for training and was completed by consultants. Midazolam, mivacurium, atropine, and steroid administrations were comparable between the two groups.

The underlying diagnoses of respiratory impairment (noted after RB) are listed in Table 2. Additionally, there were two patients with a diagnosis of ventricular septal defect and West syndrome (a form of epilepsy) in Group P.

The hemodynamic parameters before and after induction and the highest and lowest values during RB are listed in Table 3. The baseline heart rate, baseline arterial pressures (systolic, mean, and diastolic), and the reduction in HR and arterial pressures after induction were comparable between the groups; however, the decrease in the mean arterial pressure from baseline values to the lowest values during RB was significantly higher in Group P ($p=0.049$). The differences in other hemodynamic parameters were comparable. No participants in either group had hypotension in two consecutive measurements or were administered ephedrine. In a 14-month-old boy in Group K, the remifentanil infusion had to be decreased due to persistent bradycardia despite atropine administration, and other

Table 2 - Diagnosis after rigid bronchoscopy.

	Group P	Group K
Foreign body aspiration	10	11
Organic	*6*	*9*
Non-organic	*4*	*2*
Pneumonia	2	3
Bronchiectasis	1	0
Asthma	1	0
Tuberculosis	0	1
Upper respiratory tract infection	3	2
Postoperative pulmonary atelectasis	1	1
Unknown diagnosis	2	2

Values are expressed as the number of patients.

Table 3 - Hemodynamic parameters.

		Group P	Group K
HR (beats/min)	BI	129 (±26)	132 (±26)
	AI	108 (±24)	105 (±22)
	HIGH	119 (±24)	124 (±18)
	LOW	99 (±22)	107 (±21)
SAP (mmHg)	BI	98 (±15)	106 (±14)
	AI	77 (±9)	85 (±15)
	HIGH	86 (±8)	101 (±13)
	LOW	75 (±8)	90 (±14)
MAP (mmHg)	BI	77 (±13)	80 (±13)
	AI	56 (±8)	59 (±11)
	HIGH	64 (±7)	75 (±12)
	LOW*	53 (±7)	64 (±10)
DAP (mmHg)	BI	61 (±13)	66 (±13)
	AI	42 (±8)	46 (±11)
	HIGH	50 (±8)	62 (±12)
	LOW	39 (±6)	50 (±10)

Values are expressed as the mean±SD; HR, heart rate; SAP, systolic arterial pressure; MAP, mean arterial pressure; DAP, diastolic arterial pressure; BI, baseline values before induction; AI, values after induction, just before the laryngoscopy; HIGH, highest values during bronchoscopy; LOW, lowest values during bronchoscopy. *: $p=0.049$, when comparing the decreases from the baseline values.

bradycardia events in Group K were due to severe desaturation during emergence. The only atropine administration in Group P occurred during a prolonged laryngoscopy.

The emergence characteristics are listed in Table 4. After decreasing RI to 0.05 μg/kg/min, the time to extubation (A) was comparable between the two groups, but the incidence of controlled and/or assisted mask ventilation (B) and the duration of mask ventilation (C) after extubation were significantly higher in Group K. The restoration of spontaneous ventilation without assistance (D=A+C) and eye opening (E) were comparable between the groups.

The adverse events are listed in Table 5. The differences in the incidences of adverse events were not statistically significant. The number of desaturation episodes during the procedure is listed in Table 6. Four patients in Group P and five patients in Group K experienced mild desaturation, while one patient in Group P and one patient in Group K experienced moderate desaturation at room air before the procedure. Four patients in Group P and eight patients in Group K experienced 4 and 12 episodes of desaturation, respectively, during the procedure ($p>0.05$). One patient in Group P and five patients in Group K had severe desaturation episodes ($p>0.05$). Severe desaturation episodes during induction and laryngoscopy were of short duration. The desaturation incidence that occurred during bronchoscopy was due to a fragmented organic foreign body, and the other incidences were due to bronchospasm. All patients were transferred to the recovery ward with SpO_2 values above 94% with or without supplemental oxygen.

DISCUSSION

The addition of a ketamine infusion to anesthesia with a remifentanil infusion has been previously investigated, and the results demonstrated hemodynamic stability and less frequent adverse events, such as bradycardia and hypotension (12-14); however, the combined use of remifentanil and ketamine without any other adjuvant was not previously investigated. In this study, the hemodynamic effects of

Table 4 - Emergence characteristics.

	Group P	Group K	*p*
A- Time to extubation* (min)	18.7 (±5.9)	15.1 (±6.9)	NS
B- Controlled and/or assisted mask ventilation** (*n*)	4	13	0.0095
C- Duration of mask ventilation** (min)	0.55 (±1.3)	6.65 (±10.3)	0.001
D- Time to spontaneous ventilation without assistance* (min)	19.2 (±5.8)	21.7 (±11.2)	NS
E- Time to eye opening* (min)	27 (±9.1)	30.2 (±16)	NS

Values are expressed as the mean (±SD) or number of patients (*n*).
*: After decreasing the remifentanil infusion to 0.05 μg/kg/min.
**: After extubation.
NS: not significant.

bolus propofol and ketamine as adjuvants to remifentanil-based anesthesia for RB in pediatric patients were compared. With regard to the decline in mean arterial pressures from baseline values to the lowest values during RB, ketamine seemed slightly more advantageous than propofol. If we had used lower remifentanil infusion rates and higher doses of adjunct drugs (propofol or ketamine), the difference in hemodynamic parameters may have been more significant. In addition, the incidence of hypotension and bradycardia was low in both groups, likely due to the high sympatho-adrenal stimulation of RB.

Regarding emergence characteristics, the need for mask ventilation and the duration of mask ventilation after extubation were higher in Group K. This finding may be due to the longer duration of action of ketamine and the maintenance of remifentanil infusion during emergence, which may cause apnea. Airway reactions after extubation may be another explanation. As the remifentanil-ketamine combination is a less common anesthesia technique, different clinical features of ketamine (dissociative anesthesia) may also cause confusion among anesthesiologists regarding the appropriate timing of extubation.

Despite its bronchodilating capabilities and fewer respiratory depressant properties, ketamine has been associated with laryngospasm, increased oral secretions, and alterations in pulmonary artery pressure, pulmonary vascular resistance, and oxygen consumption (7-9), which may explain why Group K patients had more desaturation episodes during the RB procedure. A higher sample size may demonstrate significant differences in the incidence of desaturation. An antisialagogue premedication may have been beneficial in Group K.

Adjunct remifentanil use during RB with propofol or inhalational anesthetics along with either spontaneous or controlled ventilation has been described previously (15-21). The infusion rates of remifentanil were 0.5 μg/kg/min or lower in those studies. A similar protocol as that used in Group P was used for general anesthesia with controlled ventilation during RB of adult patients with American Society of Anesthesiologists (ASA) physical status III, but with relatively lower infusion rates of remifentanil (0.5 μg/kg/min), a propofol infusion, and 0.25 mg/kg mivacurium (16). A 0.3-1 μg/kg/min remifentanil infusion and propofol infusion with muscle relaxants during endolaryngotracheal surgery in pediatric patients have also been described, but the hemodynamic parameters were not reported (21).

There are several acceptable general anesthesia techniques for RB. Although inhalation anesthesia with spontaneous ventilation is the most popular technique (22), there is no strong evidence for the superiority of this technique for RB. There are limited data on TIVA and controlled ventilation for pediatric RB. The use of inhalation anesthetics during RB is a major risk factor for the exposure of operating room personnel to anesthetics (23), while TIVA is the definite solution to this problem. In addition, immobilization of the patient and controlled ventilation allow for suitable laryngoscopy and RB conditions (22,24).

The skill and experience of the endoscopist (as well as the anesthetist) are crucial for preventing adverse events and complications during RB and foreign body removal. Non-experienced endoscopists, as was the case in this recent study, may sometimes initiate RB for training purposes.

Table 5 - Adverse events.

	Group P	Group K
Midazolam-related agitation	1	1
Bradycardia		
During laryngoscopy	1	0
During bronchoscopy	0	1
During emergence	0	2
Total	1	3
Hypotension		
After induction	3	3
During bronchoscopy	2	0
Total	5	3
Movement during RB		
Mild	9	12
Moderate	0	0
Severe	0	0
Severe desaturation	1	5
Bronchospasm	0	2
aryngospasm	0	1
Postoperative nausea and vomiting	1	4
Emergence agitation	1	3

Values are expressed as the number of patients.

Table 6 - Desaturation episodes.

	Group P			Group K		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Before procedure	4	1	-	5	1	-
During induction	-	-	1	3	-	1
During laryngoscopy	1	-	-	1	1	1
During bronchoscopy	1	1	-	1	-	1
Before extubation*	-	-	-	-	-	1
After extubation	-	-	-	-	1	1
Total during procedure	2	1	1	5	2	5

Values are expressed as the number of episodes.
*: After decreasing remifentanil infusion to 0.05 μg/kg/min.

Prolonged laryngoscopy, traumatic insertion of the rigid bronchoscope, and dislodgement of the foreign body may cause serious adverse events, while a relaxed glottis and abducted vocal cords may simplify laryngoscopy, bronchoscope insertion, and foreign body removal (22,24). Coughing and movement of the patient (even respiratory movement) may have a negative impact on the concentration of the endoscopist (especially in non-experienced physicians) and could increase morbidities, such as airway injury, pneumothorax, or hemorrhage; thus, immobilization is crucial (22,24). For these reasons, once adequate mask ventilation is established, controlled ventilation is usually our technique of choice in RB. In this study, while complete immobilization during RB was achieved in only half of the patients, there were no movements affecting surgical comfort and outcome. There are many studies describing successful intubation with remifentanil without the use of a neuromuscular blocking agent (25). This study may have been performed without the use of neuromuscular blocking agents; however, this may have increased the use of adjuvants and changed the hemodynamic and emergence characteristics. To prevent the need for antagonists and their adverse effects, we aimed to limit the use of mivacurium. Acceptable muscle relaxation and immobilization was achieved in both groups with a total dose of 0.18 mg/kg of mivacurium, which is administered at a standard dose of 0.25 mg/kg for endotracheal intubation of children (26). A lack of neuro-muscular monitoring may be a weakness of this study.

Maintaining the remifentanil infusion during emergence from anesthesia and tracheal extubation has been described previously (27). This technique was used after propofol-remifentanil anesthesia in adult patients and was found to reduce hemodynamic changes and coughing associated with extubation. Opioid-based TIVA or maintenance of the remifentanil infusion during extubation is our technique of choice for children with a high risk of airway reactions. It is reasonable to ignore extended emergence times when aiming to decrease the incidence of airway reactions in high-risk patients. Based on the emergence characteristics in our study, this technique may not be suitable for ketamine anesthesia.

Intermittent propofol injections instead of continuous infusion during rigid bronchoscopy may be preferred as a practical technique in some centers (17,28), as in our institution. In this study, to decrease the recovery time and risk of awareness, propofol or ketamine infusions instead of bolus doses and bispectral index monitoring may be more appropriate. However, Bould et al. (28) found no difference in the bispectral index (BIS) values of patients anesthetized for elective RB with intermittent boluses or target controlled infusions of propofol. In addition, bispectral index monitoring was found to be unreliable in the case of ketamine use (29).

In conclusion, remifentanil-based TIVA with propofol or ketamine as an adjuvant drug along with controlled ventilation is a viable technique for pediatric RB. The intense stimulation associated with RB was well suppressed with a 1 μg/kg/min remifentanil infusion, which also secured hemodynamic stability. Propofol appeared to be more suitable in the recovery period of remifentanil-based anesthesia for RB of pediatric patients, while ketamine use instead of propofol did not provide a definite advantage when hemodynamic stability during RB is considered.

AUTHOR CONTRIBUTIONS

Bakan M designed and conducted the study, analyzed the data, and wrote the manuscript. Topuz U designed and conducted the study. Umutoglu T helped writing the manuscript. Gundogdu G conducted the study and analyzed the data. Ilce Z conducted the study. Mehmet Elicevik conducted the study and helped writing the manuscript. Kaya G helped writing the manuscript.

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