

## **Reduced incidence of Laryngospasm with Remifentanil-Midazolam Anaesthesia compared to Halothane-Fentanyl**

Shahriari Ali

Department of Anesthesiology, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran.

### **Abstract**

**Objective:** To compare the incidence of laryngospasm by using halothane-fentanyl anaesthesia and midazolam-remifentanil anaesthesia in paediatric patients undergoing eye surgery.

**Methods:** We enrolled 120 ASA physical status I children aged 7-12 years scheduled for eye surgery from March 2004 to February 2006 in this prospective clinical trial study. Children suffering from any medical condition that could affect airway reflexes such as active upper respiratory infection, symptomatic asthma, obesity, patients with predicted difficulty in tracheal intubation were not included in the study. Patients with prolonged or difficult intubation or those who received another drug before extubation were excluded from the study. Using a random numbers table, participants were allocated to two equal groups. After induction of anaesthesia, in one group Halothane 1% was administered for the maintenance of anaesthesia in addition with intravenous fentanyl 1.5 µg kg<sup>-1</sup>, and for the patients of the other group midazolam with a dose of 0.1 mg kg<sup>-1</sup> and remifentanil infusion by a dose of 0.1 µg kg<sup>-1</sup> min<sup>-1</sup> was administered. The patients were extubated in a unique plan of anaesthesia, using the sign of swallowing as a clinical indicator for extubation of patients.

**Results:** The incidence of laryngospasm was lower in midazolam-remifentanil group (0%) in comparison with halothane-fentanyl group (6.6%).

**Conclusion:** The results of our study suggest that remifentanil combined with midazolam in children undergoing eye surgery provided a better condition for extubation of the patients (JPMA 58:111;2008).

### **Introduction**

Laryngospasm and airway complications such as coughing, and oxygen desaturation are serious complications after tracheal extubation in paediatric patients and may lead to some morbidity like desaturation, bradycardia, pulmonary oedema, and pulmonary aspiration.<sup>1</sup> This latter complication is especially significant as it may cause serious morbidity, and the patient may require intubation, ventilation and management in an intensive care setting.<sup>2</sup> Risk factors include difficult intubation, nasal, oral or pharyngeal surgical site, and obesity; however, it may occur unexpectedly in any patient.<sup>3</sup> Patient movement, surgical stimulus, irritant volatile agents, and failure to deliver the anaesthetic can be the precipitating factors of laryngospasm.<sup>1</sup>

The aim of this study is to compare the incidence of laryngospasm and airway complications in paediatric patients at the same depth of anaesthesia, using signs of swallowing as a clinical indicator for extubation, by using different agents for the maintenance of anaesthesia, halothane (a nonpungent volatile anaesthetic) and midazolam and remifentanil (two intravenous agents). This comparison was not reported in previous studies.

### **Patients and Methods**

From March 2004 to February 2006, 120 ASA

physical status I children aged 7-12 years, undergoing elective eye surgery were studied. The present prospectively designed study was approved by the ethics and clinical studies committee of Zahedan University of Medical Sciences and informed and signed consent was obtained from the parents of all the patients who were enrolled in the study.

Children suffering from any medical condition that could affect airway reflexes such as active upper respiratory infection within one week before surgery, lower respiratory tract infection (productive cough and fever > 38.3°C) within 4 weeks before surgery, symptomatic bronchial asthma, history of moderate to severe asthma or residual lung disease of prematurity, obesity (>50% of ideal body weight) were not included in the study. Also patients with predicted difficulty in tracheal intubation and patients admitted for strabism surgery were not included in the study.

Patients with prolonged or difficult intubation (more than 15 seconds) or those who received another drug before extubation as lidocaine or a supplemental dose of narcotics were excluded from the study.

All children were admitted on the day of surgery and fasted for at least six hours prior to surgery. All children received an oral medication for sedation (1 mg/kg<sup>-1</sup> hydroxyzine) one hour before anaesthesia.

Using a random numbers table, participants were randomly allocated equally to either halothane-fentanyl group (group H) or midazolam-remifentanyl group (group R). After arrival in the operating room and intravenous (IV) access, infusion of crystalloid solution was started. In all patients, induction of anaesthesia was started with atropine 0.01mg kg<sup>-1</sup>, thiopentone 4 mg kg<sup>-1</sup>. Neuromuscular blockade was obtained with atracurium 0.5 mg kg<sup>-1</sup>. An uncuffed tracheal tube was inserted and the lungs were ventilated with N<sub>2</sub>O and oxygen. A wet gauze was inserted into the pharynx for prevention of extreme leakage of delivered gas around the tube. Controlled ventilation was adjusted to maintain ETCO<sub>2</sub> between 34-38 mm Hg. Immediately after intubation, for patients assigned to the midazolam/remifentanyl group, midazolam was administered with a dose of 0.1 mg kg<sup>-1</sup> and then remifentanyl was administered at a rate of 0.1 µg kg<sup>-1</sup> min<sup>-1</sup>. For patients assigned to the halothane-fentanyl group, a dose of 1.5 µg kg<sup>-1</sup> of fentanyl and halothane 1% was administered for the maintenance of anaesthesia. Dexamethasone 0.1mg kg<sup>-1</sup> was administered for all patients. At the end of surgery, residual neuromuscular blockade was antagonized with neostigmine and atropine.

Continuous monitoring included heart rate, non-invasive arterial blood pressure measurement, pulse oximetry, continuous ECG, BIS, and end-tidal carbon dioxide concentrations. Recovery times were determined at 1-minute intervals from discontinuation of the maintenance anaesthetics to awakening (opening eyes). Two anaesthetists, of various grades and experience, with more than 8 years work experience were responsible for the management of anaesthesia, intubations and extubations in this study. The presence of any complication after extubation including laryngospasm (with SpO<sub>2</sub> < 85% for more than 10 sec) was recorded by a research nurse, who was blinded to the anaesthetic drug and technique used. Positive airway pressure by a face mask and intravenous lidocaine or succinylcholine (if required) was planned for the treatment of laryngospasm.

Power analysis had revealed that 48 patients needed to be recruited to each limb of the study to detect a change in laryngospasm of 5%, which was believed to be clinically significant, with a power of 0.9 and a p value of 0.05. Sixty patients were recruited into each group to allow for dropouts.

Data were expressed as mean (±SD). Demographic values were analyzed with the 2 test and one-way analysis of variance. The values of heart rate, mean arterial pressure and the incidence of laryngospasm were analyzed using Student's t-test for independent groups; P<0.05 was considered statistically significant.

## Results

Data were collected from 120 patients, aged 7-12 yr. The patients' characteristics are shown in Table 1. No statistically significant differences among the groups were seen in age, weight, duration of surgery, and the value of BIS (between 40 and 50 in all patients).

Laryngospasm did not occur in any patients of remifentanyl-midazolam group, while 4 patients (6.6%) in halothane-fentanyl group experienced laryngospasm.

**Table 1. Patients demographic data in Halothane-fentanyl group and Remifentanyl-midazolam group.**

Variables	Halothane*	Remifentanyl **
Age (year)	9.3±2.1	9.6±2.6
Weight (kg)	21.6±7.5	22.57±7.9
Surgery duration (min)	45.5± 12	50± 15

\*Halothane-fentanyl group  
\*\* Remifentanyl-midazolam group

**Table 2. The frequencies of complications after surgery, and the time between reversing of neuromuscular blocking and eye opening among patients of two groups.**

Events	Halothane group*	Remifentanyl group**	P value
coughing	5 (8.3%)	0 (0%)	<0.05
Breath holding	0 (0%)	0 (0%)	1
Laryngospasm	4 (6.6%)	0 (0%)	<0.05
Nausea and vomiting	0 (0%)	0 (0%)	1
Time to eye opening(min)	13.4 ± 2.8	2.5 ± 1.3	<0.05

Note: The values in the first four rows are represented as n (%).  
\*Halothane-fentanyl group  
\*\* Remifentanyl-midazolam group

Laryngospasm was managed by administration of 100% oxygen with continuous positive airway pressure through a tight fitting face mask and intravenous lidocaine 1mg kg<sup>-1</sup>. No serious complications (bradycardia or others) were observed. Nausea and vomiting did not occur in any patients in this study (Table 2).

## Discussion

Laryngospasm is commonly perceived to be a significant problem by anaesthetists, with an incidence of 0.78%-5% depending on surgical type, patient age, pre-existing condition, and anaesthetic technique.<sup>4</sup>

We found no laryngospasm in remifentanyl-midazolam group compared to the frequency of 6.6% laryngospasm among patients in halothane-fentanyl group.

The depth of anaesthesia and anaesthetic factors such as the choice of volatile anaesthetic drug, use of opioid analgesics, and age of the patient may contribute to airway hyperreactivity and laryngospasm during extubation.

We designed an identical plan for extubation of all patients: the sign of swallowing as a clinical indicator for extubation of patients, which means the patients were extubated in a nearly light plain of anaesthesia.

It has been suggested that the incidence of laryngospasm is reduced by either tracheally extubating patients in a deep plain of anaesthesia or in a virtually conscious state.<sup>1</sup> Leicht et al.<sup>2</sup>, Lee et al.<sup>5</sup>, and Koc et al.<sup>4</sup> used awake tracheal extubations for their studies but all reported a frequent incidence of laryngospasm (between 21% and 27%) in the control groups of post tonsillectomy patients. A potential advantage of deep tracheal extubation, as opposed to awake extubation, is that patients are less likely to cough and strain afterward, thus avoiding the likelihood of laryngospasm and oxygen desaturation.<sup>6</sup> Coughing and straining can also cause the rupture of sutures in the patients undergoing eye surgery. Although deep extubation might afford some protection against such responses, the risk of aspiration and inadequate airway protection during this vulnerable period remains a primary concern, because there is evidence that the incidence of respiratory complications is more frequent when the trachea is extubated in a deep plain of anaesthesia.<sup>1</sup> In a recent study, Gulhas et al.<sup>3</sup> used deep tracheal extubation in posttonsillectomy patients and reported a frequent incidence of laryngospasm (25%) in the control group where magnesium was used in an attempt to decrease the incidence of laryngospasm.

We used uncuffed tracheal tube in our study, because our previous experience has shown that tracheal intubations with uncuffed tubes were associated with lower incidence of laryngospasm.

The higher incidence of laryngospasm in halothane-fentanyl group can be due to the longer recovery of halothane as an anaesthetic agent, or to the fact that halothane directly causes airway hyperreactivity.

Walker et al. found a higher frequency of airway complications such as laryngospasm and coughing with halothane compared to patients anaesthetized with sevoflurane.<sup>7</sup>

Pounder et al. found in their study that the incidence of respiratory complications and oxygen desaturation were comparable between isoflurane and halothane study groups when tracheal extubation occurred in the anesthetized state.<sup>8</sup> Pappas et al. found that awake LMA removal during isoflurane anaesthesia results in a higher incidence of adverse airway events and isoflurane carries a risk of severe airway hyperreactivity and critical events when compared with sevoflurane.<sup>9</sup>

Previous studies confirm that isoflurane can cause

airway hyperreactivity, and the results of our studies suggest that halothane has some effect too.

Powerful synthetic opioids like fentanyl used in anaesthesia can cause muscle rigidity. Rigidity classically occurs with the use of high-dose opioids during induction of anaesthesia in the non-paralyzed patients. Rigidity can also occur during emergence from anaesthesia. Roy reported a case of fentanyl-induced rigidity during emergence from general anaesthesia with low dose of fentanyl.<sup>10</sup> Since opioid-induced rigidity classically appears at induction before the trachea is intubated, the principal problems are related to difficulties in ventilation. Originally, thoraco-abdominal rigidity was believed to account for the ventilatory problems; however, studies suggest that glottic closure is more likely to be the responsible mechanism.<sup>11-13</sup> Fentanyl has been also shown to inhibit central sympathetic outflow causing vagal predominance, inducing cough and reflex bronchoconstriction.<sup>14-16</sup> But whether the laryngospasm in the Halothane-fentanyl group in our study was due to fentanyl, or the halogenated agent, is a concern. It can be suggested that the airway hyperreactivity due to the volatile anaesthetic is the major cause of laryngospasm. This can be confirmed by other reported studies: Kong et al. found that pretreatment with fentanyl reduces the incidence of airway irritation during inhalational induction of anaesthesia with sevoflurane.<sup>17</sup> Lee et al. also observed that fentanyl reduces desflurane-induced airway irritability in children.<sup>18</sup> Tagaito et al reported that incremental doses of fentanyl depress airway reflex responses in a dose-related manner.<sup>19</sup> Our previous experience has shown that by using a higher dose of fentanyl and a lower dose of halothane, there was lower incidence of laryngospasm.

Postoperative nausea and vomiting (PONV) is a very important adverse event, which affects discharge following ambulatory surgery. The incidence of PONV after the administration of general anaesthesia without antiemetic prophylaxis is reported to be between 35% and 68%.<sup>20</sup> In the present study, the frequency of PONV in both groups was small, a finding that may be related to the premedication (hydroxyzine) or dexamethasone administered to the patients.

The study concluded that remifentanyl combined with midazolam used in children undergoing eye surgery, provided better results of extubation with a lower risk of laryngospasm.

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