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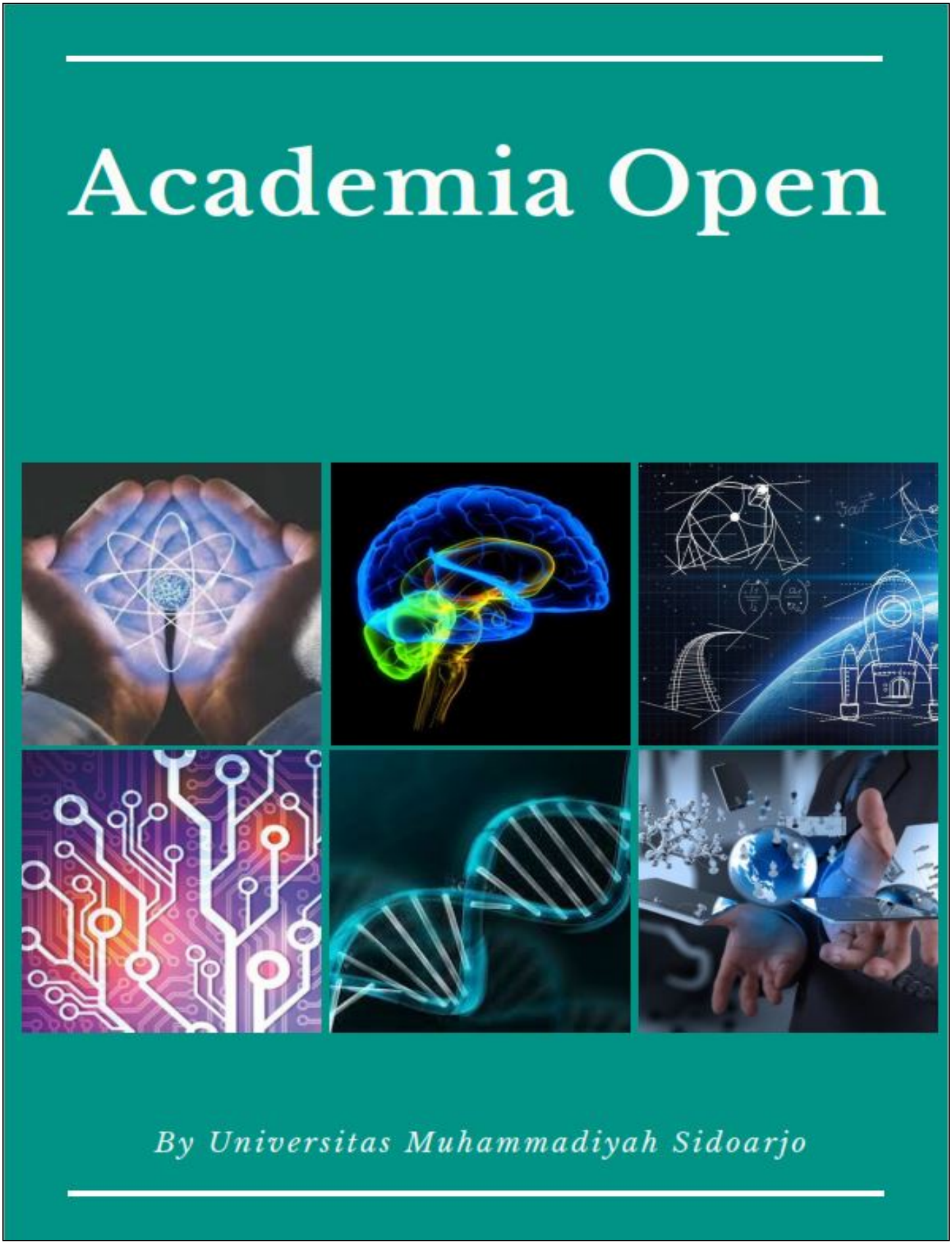

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Impact of Sevoflurane and Propofol on Pediatric Laryngeal Reflexes During Anesthesia Induction

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Abstract

This study aimed to investigate the influence of sevoflurane and propofol anesthesia, administered at two distinct levels of hypnosis, on laryngeal reflexes in children aged 2 to 6 undergoing surgery. Seventy participants were randomly assigned to receive either sevoflurane or propofol anesthesia, and their responses to laryngeal irritation were evaluated. Results revealed that regardless of the level of hypnosis, sevoflurane anesthesia led to a higher incidence of laryngospasm apnea compared to propofol anesthesia, with some episodes lasting over five seconds. Conversely, children receiving propofol anesthesia exhibited more frequent exhalation and coughing responses. These findings highlight the importance of appropriate anesthetic dosages in pediatric cases, as the choice of anesthetic agent can significantly impact airway defense reflexes, with potential clinical implications for airway management during anesthesia induction in children.

Highlights :

- Sevoflurane anesthesia in children aged 2 to 6 is associated with a higher incidence of laryngospasm apnea compared to propofol anesthesia, emphasizing the need for careful anesthetic selection in pediatric cases.
- Propofol anesthesia induces more frequent exhalation and coughing responses, suggesting potential advantages in airway management during anesthesia induction in children.
- This study underscores the critical role of appropriate anesthetic dosages in mitigating the risk of exaggerated airway defense reflexes and ensuring patient safety during pediatric surgery.

Keywords : Pediatric anesthesia, Sevoflurane, Propofol, Laryngeal reflexes, Airway management

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Introduction

Coughing, apnea, laryngospasm, and exhalation reflex all play a part in defending the lower airways against aspiration - a crucial defense mechanism. An excessive upper airway reflex known as laryngospasm can provide protection against aspiration but also poses the risk of serious damage[1]. Though clinically significant, there is limited data on the quantitative and qualitative aspects of these reflexes during anesthesia in humans[2]. Children tend to experience more frequent and severe apnea and laryngospasms due to respiratory reflex stimulation, which results in continuous hypoxemia[3],[4]. Despite the frequent use of agents for pediatric anesthesia, the effects on laryngeal reflexes remain comparatively unexplored[5],[6]. In this study, we aimed to examine the respiratory response and laryngeal reflex in children between the ages of 2-6 who were under propofol or sevoflurane anesthesia, based on their level of hypnosis[7]. We utilized a stimulation technique that has previously been used on adults. As part of our randomized controlled trial, we tested whether the occurrence of apnea due to laryngeal irritation was the same under sevoflurane and propofol when used for bronchospasm controlled anesthesia as we measured the two-spectrum index (BIS) scale. We also hypothesized reduced laryngeal response with increased hypnotic levels.

Method

From February 2020 through December 2022, two hospitals - Imam Sadiq Teaching Hospital and Al Hilla General Teaching Hospital - geared up for a number of operations on a special group of children. These procedures were set to involve seventy young kids, all between the ages of 2 and 6 years. It was mandatory that written consent be provided by the children's parents before any operation could commence. Naturally, not every child was eligible. For instance, those with neurological or respiratory complications, a family history of malignant hyperthermia, or a prior diagnosis of cardiopulmonary issues were excluded from the study.

Patients were randomised at random to receive propofol or sevoflurane, and the levels of hypnosis were BIS ±40, then BIS± 60, or BIS ±60, then BIS ±40.

Anesthesia and preparation of patient

Premedication consists of rectal or oral midazolam 0.3 mg/kg 10 to 20 minutes before anesthesia. Electrocardiography, noninvasive blood pressure measurements, capnography, and pulse oximetry are used for routine monitoring. Real-time BIS data acquired by EEG

Record the average value every 5 s using a computerized data logging system. All patients were anesthetized through a mask containing 70% nitrous oxide and 30% oxygen. Immediately after peripheral venous access was established, the supply of nitrous oxide was interrupted and the flow of fresh air was set at 6 L/min. Oxygen is supplied through a semi-closed anesthesia circuit throughout the procedure. All patients breathed spontaneously throughout the study. The depth of anesthesia was increased in the propofol group, with an initial bolus dose of 3 mg/kg, followed by an additional bolus dose (1 mg/kg) as needed, and anesthesia was induced in the sevoflurane group at an inhalation rate of 8%. When a sufficient depth of anesthesia has been achieved and cannot respond to safe manipulation of the jaw, the LMA is inserted. Thereafter, maintenance anesthesia (propofol infusion or sevoflurane inhalation) was adjusted to achieve the first randomized hypnotic level (BIS). 40+\- 5 or up to 60+\-5). Continuous measurement of end-tidal carbon dioxide using a calibrated lateral flow meter

The fiber optic borescope connected to the camera passes through the membrane of the corner connector. The position of the head of the bronchoscope allows the opening of the larynx to be seen

All data, including video images, are stored simultaneously in digital format using custom laboratory views.

Laryngeal stimulation

The tip of an epidural catheter (20 gauge) is positioned above the level of the glottis after being inserted through the endoscope's suction channel. Through the catheter, 0.2 ml of distilled water was injected into the laryngeal mucosa around the voice cords to elicit airway reflexes. Prior recordings included breathing responses and continuous endoscopic views. both before and after stimulation.

Experimental Procedure

The larynx was sequentially stimulated in each patient to induce hypnosis at various levels. based on the available opportunity: a superficial hypnotic level with BIS 60 ±5 or a deeper hypnotic level with BIS 40 ±5. After confirming that respiratory parameters were stable and the BIS values were stable within the range of the given level, laryngeal stimulation was carried out at least five minutes later..

Emergency procedures for laryngospasm include using a jaw thrust and continuous positive airway pressure (10 cm

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H2O) for laryngospasms lasting more than 10 seconds[10],[11] . When these procedures fail to solve the issue or saturation (SpO2) falls to 90% or less, atropine and succinylcholine are administered intravenously at a dose of 1 mg per kilogram of body weight.

The respiratory responses resulted from laryngeal stimulation are categories into seven groups[8]

[1]defined as complete pharyngeal closure on video frames longer than 5 seconds, [5] cough reflex, [6] Exhalation reflex, [2] defined as complete closure of the glottis on-image video lasting more than 10 seconds, and [7] spasmodic panting, [3] defined as apnea with incomplete closure of the glottis lasting more than 5 seconds and [4] central apnea cases without complete glottis closure over video frames lasting more than 10 seconds. Identifying apnea episodes, measuring the duration of exhalation reflex breaks, and pinpointing intervals between vocal cord mucosa stimulation were all assessed[9]. Respiratory reflex response duration was also measured for stable respiratory patterns. Evaluating events within a 3-minute laryngeal stimulation window for both patient group and hypnosis level were recorded[12].

Statistical analysis

The data on demographics and procedures underwent scrutiny for normal distribution through the utilization of the Shapiro-Wilk test[13]. The results of this analysis were reported as either the mean or standard deviation. Continuous or categorical variables that were measured repeatedly were examined via regression techniques[14]. The regression model included independent variables such as the assignment of patient groups, the factor of repeat measurement (hypnic level), and the interactions between these two factors. As the panting rate was low, Fisher's exact test was employed to analyze this variable[15]. The intent-to-treat approach was used for all analyses. Any p-values that were less than 0.05 were deemed statistically significant[16]

Results and Discussion

Results

Studied were a total of seventy sprightly kids, aged from 2 to 6 years, who opted for surgery or dental work under a general anesthetic[17]. Population specifics are highlighted in Table 1, with initial details being relatively consistent, yet males prevailing in both groups. The sevoflurane cohort comprised of patients who underwent laryngeal stimulation in accordance with protocol, except for one person who was not considered for the study after experiencing protracted laryngospasm post-stimulation[18]. However, succinylcholine was administered to rectify the situation immediately. Three patients in the propofol group were unable to achieve clinical stability prior to the first stimulus. One patient had a persistent cough, another had self-limited recurrent short laryngeal spasms, and the third patient had no stable degree of coma[29]. As a result, laryngeal stimulation should not be performed in these patients. Additionally, digital data for one patient were not available for analysis due to an error in the data storage system. This group ultimately had 31 subjects available for detailed video analysis[20]. Table 1 displayed comparable BIS values (BIS 40:39-3 and BIS 60:58 4, as well as electromyogram) for both groups, despite the drugs administered. The respiratory and hemodynamic qualities are indicated in Table 2. The measured variables revealed variations in breathing, minute ventilation, and heart rate between the two hypnosis stages. Interestingly, the sevoflurane group exhibited significantly increased minute ventilation and heart rate when compared to the propofol group. While the end tidal carbon dioxide maintained no statistically significant differences, the sevoflurane group's ventilation system upheld a consistent level of 32 dB throughout the experiment. Figure 1 sums up the impact of both drugs on respiratory reflexes, highlighting the types and rates of reflex responses analyzed in two different groups - propofol and sevoflurane - at varying levels of hypnosis, namely BIS 40 and BIS 60. Interestingly, the sevoflurane group experienced a significantly higher occurrence of complete glottis closure, even with varying degrees of hypnosis, compared to the propofol group. The difference between these two groups was more pronounced than the group that exhibited instances of laryngospasm[21]. Laryngeal closure lasting more than 10 seconds was examined through video analysis of two groups. It was observed that the closure of the glottis occurred mainly in the pseudo-cord and was not limited to the vocal cords. No significant difference was found between the two groups or their levels of hypnosis for shorter and longer central apnea, although there were a range of laryngeal responses that varied from glottis expansion to minor opening at the glottis level of pars intercartilaginea of the vocal cords. Laryngeal stenosis also served as an indicator of flexibility change during apnea episodes. Under superficial hypnosis, the propofol group exhibited significantly more cough and exhalation reflexes compared to the other group[22]. There were no significant interaction coefficients observed between the patient groups and their level of hypnosis. However, the incidence of these reflexes was incredibly infrequent in the propofol group, with only 5% of them experiencing it. It is plausible that this disparity was due to mere chance. In terms of cumulative apnea duration, the sevoflurane crew experienced longer interruptions with expiratory reflexes compared to the propofol team (13.7 ± 18.2s versus 6.7 ± 7.8s; P 0.017). Strangely enough, both groups were equally hypnotized (P =0.7). After laryngeal stimulation, it was discovered that the duration of respiratory reactions varied depending on anesthesia level. Comparing the two groups, it was noticed that normal breathing was restored faster after stimulation for BIS 40 than BIS 60. The propofol group had 31± 29.3 seconds and 57.1± 57.8 seconds, while the sevoflurane group had 22.4 ±35.9 seconds and 37.5 ±55.7 seconds, respectively (P=0.002). Interestingly, there was no detectable difference between the groups (P= 0.19). In 18 out of 19 cases where patients had laryngospasm lasting longer than 10 seconds, the implementation of forceful jaw movement and

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consistent active breathing brought about effective reduction of laryngospasm[23]. However, 1 patient from the sevoflurane group required administering succinylcholine to combat the laryngospasm. Among patients in the sevoflurane group, 3 experienced desaturation (SpO2 90%), while 4 in the propofol group had the same effect. Desaturation in all cases was transient and not accompanied by bradycardia, except in cases with continual apnea due to laryngospasm. In the sevoflurane group, 11 patients experienced sudden movement of the limbs after external stimulation, and in the propofol group, 22 patients experienced the same.

Demographic data	Propofol Group	Sevoflurane Group
Age, year	4.6 (3.6, 5.4)	4.7 (3.2, 6.0)
Weight, kg	18.9 (16.0, 21.0)	18.5 (15.0, 22.0)
Male/female, n	27/8	27/8
Height, cm	109 (102, 114)	109 (98, 120)
Propofol infusion,Mg . kg-1 . min-1BIS 40	223 (206, 258)	0
BIS 60	134 (121, 145)	0
ET sevoflurane, %BIS 40	0	2.4 (1.9, 2.7)
BIS 60	0	1.3 (1.1, 1.5)

Table 1. *Demographic Data and Administered Drugs*

Data are presented as median BIS = Bispectral Index score

Discussion

When pediatric patients aged 2-6 years are anesthetized with propofol or sevoflurane and exposed to laryngeal stimulation, varying degrees and types of laryngeal reflexes can occur, such as contractions, laryngospasm, central apnea, cough reflex, panting spasm, and apnea. Surprisingly, there were significant differences between the rates of respiratory and laryngeal reflex responses following laryngeal stimulation, which contradicted our hypothesis. The primary parameter of interest, apnea with laryngospasm, was more frequent with sevoflurane use. Conversely, the rates of cough and expiratory reflex were higher with propofol use. Additionally, the occurrence of apnea with laryngospasm, central apnea, and cough reflex seemed to be unaffected by the degree of hypnosis (BIS 40 vs. 60).

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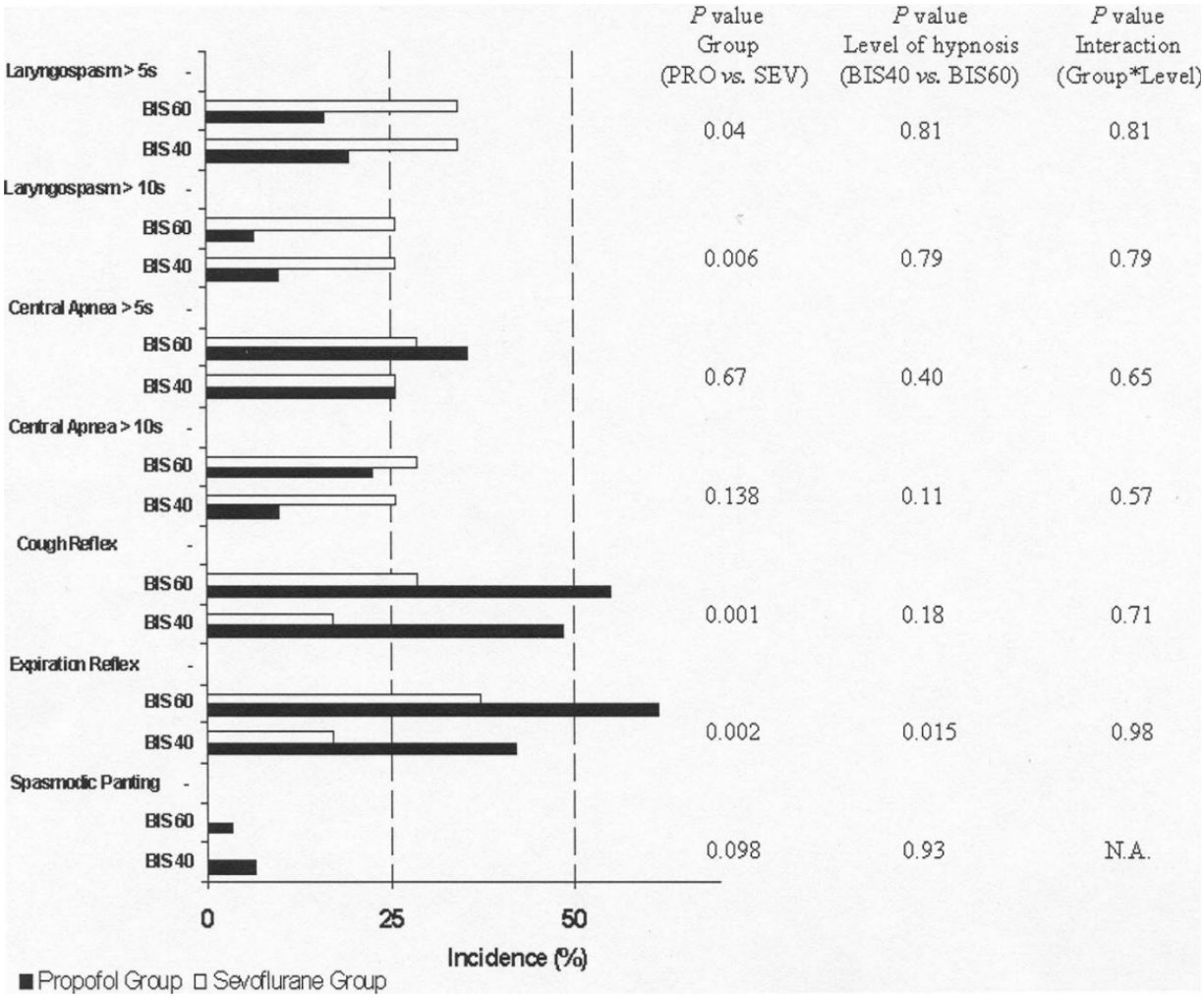

Figure 1. *Incidences of various types of laryngeal and respiratory responses to laryngeal stimulation in the propofol (PRO) and sevoflurane (SEV) groups. Statistical analyses examined effects of the anesthetic drug, the level of hypnosis, and their interaction (Group * Level). For the reflex "spasmodic panting," the interaction could not be calculated. BIS =Bispectral Index score.*

Comparison the response of laryngeal and respiratory reflexes

Laryngeal stimulation has been modeled by Tagaito et al., and elicited responses have been sorted by consistent categories in adult subjects, according to Tanaka et al. However, when children are the focus of this model, the reflex responses must adhere to specifications that are pertinent to that specific group. Apnea, the temporary cessation of breathing, presents differently in children and adults due to variances in body size and metabolism. This condition, also known as obstructive sleep apnea, can occur briefly in children for up to 5 seconds at a time, and has been found to have different physiological implications. To account for this, our study analyzed data on apnea that included laryngospasm, central apnea lasting more than 5 seconds, as well as episodes lasting more than 10 seconds, using a definition typically utilized in adult studies.

In patients who were anesthetized with sevoflurane, a study discovered that apneas with laryngospasm were more common. Additionally, the difference between treatment groups was more evident in longer events (10 s) than in short-lived ones (5 s). This study's primary finding demonstrates the correlation between sevoflurane and ideations of laryngospasms.

In children who were given sevoflurane for anesthesia, there was a higher occurrence of longer-lasting laryngospasm events compared to those who received other drugs, although the duration varied among all patients. Video analysis also showed apnea with incomplete laryngeal closure present in both groups after laryngeal stimulation. The presence of a central respiratory drive may not be relevant on its own as long as the airway stays open, yet if there's a concurrent laryngeal stenosis, maintaining oxygenation becomes crucial[24].

Our study was unique in its use of the laryngeal stimulation technique in pediatric patients. Unlike previous studies

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which only focused on adults under anesthesia with sevoflurane or propofol, we observed and compared laryngeal and respiratory reflexes in our young patients. Surprisingly, our findings showed a different frequency and pattern of respiratory reflexes compared to those reported in the previous studies[25]. In both groups of our study, the incidence of apnea with laryngospasm, expiratory reflex, and spasmodic wheezing was significantly lower, yet there was a higher incidence of cough in patients under propofol anesthesia. Various factors, including differences in end-tidal carbon dioxide concentration, the use of atropine and/or midazolam prior to anesthesia, and how extensively the larynx was stimulated, may explain these notable differences. Hypnotic Level Effects

It has been observed that Airway Protection Reflexes are more pronounced when a patient is only lightly anesthetized, leading to a common practice of increasing the level of anesthesia. It can therefore be assumed that as the amount of anesthesia increases, the responsiveness of the larynx should decrease[26]. However, with the exception of the expiratory reflex, there was no significant difference in the frequency of tested laryngeal and respiratory responses between the two levels of hypnosis (BIS 40 versus BIS 60; see Figure 1). This could be attributed to the fact that the difference in hypnosis levels was too small to elicit distinguishable laryngeal and respiratory reflexes. This study aimed to investigate the conditions that occur during both the induction and recovery phases of anesthesia.

variables	Group	BIS 40	BIS 60	P Value , Group (PRO vs. SEV)	P Value, Level of Hypnosis (BIS 40 vs. BIS 60)	P Value, Interaction (Group Level)
RR, breaths/min	SEV	32.4 ± 6.6	26.5 ± 6.7	0.0038	0.001	0.0003
	PRO	25.5 ± 7.2	23.5 ±7.2			
VE, ml kg^{-1} min^{-1}	SEV	138 ± 32	157 ± 28	0.0001	0.01	0.53
	PRO	123 ±25	138 ± 29			
ETCO2, mmHg	SEV	50± 5	44 ±5	0.23	0.0001	0.34
	PRO	51± 6	46 ± 5			
SpO2, %	SEV	100	100			
	PRO	100	100			
HR, beats/min	SEV	107 ±13	100 ± 13	0.016	0.0001	0.01
	PRO	97 ± 14	94 ± 14			
MAP, mmHg	SEV	53 ± 6	54 ±8	0.51	0.0001	0.01
	PRO	52 ± 8	57 ± 9			

Figure 2. *Table 2. Respiratory and Hemodynamic Variables*

BIS = bispectral index value; ETCO2 = end-tidal carbon dioxide; HR = heart rate; MAP = mean arterial pressure; PRO = propofol (n = 32); RR = respiratory rate; SEV = sevoflurane (n = 35); SpO2 = peripheral oxygen saturation from pulse oximeter; VE = minute ventilation.

During a past clinical study on kids under sevoflurane anesthesia, it was observed that even after the use of laryngeal lidocaine spray during laryngoscopy, they still had "vocal cord closure". Interestingly, this response was not matching up with the alveolar sevoflurane levels at BIS 1.2 and 1.8. However, it was observed that the length of time for respiratory responses to go back to normal was shorter when the patients were anesthetized at a lower level of hypnosis (like BIS 40 instead of BIS 60). This could be behind the common belief that deeper anesthesia leads to impaired laryngeal and respiratory reflexes[27].

The study's limitations are something that must be acknowledged. While the analysis was thorough, there were certain factors that may have affected the results. One particular concern was the restricted sample size, which could have influenced the accuracy of the findings. Additionally, there were some participants who did not submit the necessary data, which may have impacted the study's validity. Overall, it is important to consider these constraints when interpreting the study's outcomes, and further research should be conducted to address these limitations[28].

In examining the effects of propofol and sevoflurane on individuals within a stable BIS range, this research does not aim to compare commonly used clinical therapies. While this may be viewed as a limitation, focusing on BIS as a pharmacodynamic parameter allows for logical comparisons between inhaled and intravenous drugs. Interestingly, while assessing the EEG effects of general anesthesia in children over the age of 1 remains difficult, it appears to be similar to the effects found in adults. The comparison is noteworthy as it underscores the similarities in how both groups respond to anesthesia. In this study, both tested drugs were accurately predicted to impact the level of hypnosis through the use of BIS.

Spontaneously breathing patients in both groups displayed low and similar EMG activity levels according to the BIS monitor, indicating no discernible pattern of EMG activity deviating from the BIS value. This finding was further strengthened across both hypnosis levels.[23]

The usage of a laryngeal mask in procedures may lead to complications during laryngeal stimulation. It has been

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predicted that the insertion of the LMA™ might result in unmeasurable minor injuries such as swelling of receptors at the periphery of the afferent reflex arc. Furthermore, the increase in pressure within the cuff as a result of intermittent positive pressure ventilation is thought to cause soft tissue disturbances in the larynx (24.25). The findings of this study demonstrate that the procedure carries certain risks.

A study by Tanaka et al.9 observed a decrease in the effectiveness of the protective reflexes in relation to the placement of the LMA™ as time passed.

During our experience, measurements were immediately taken following induction while the LMA™ remained in place, while patients continuously breathed in an unprompted manner. With the laryngeal stimulations performed under the same circumstances, these variables could hardly sway the comparison between both drugs. The results of the study may have been impacted by the administration of midazolam to all children, with the drug itself or its interactions having an unknown effect on respiratory reflexes. However, the administration of midazolam remains commonplace in the preanesthetic stage of children and as a current standard of care..

Conclusion

Serious complications arising from exaggerated laryngeal or respiratory reflexes in pediatric anesthesia underscore the importance of appropriate dosages. Sevoflurane and propofol are commonly employed in such cases, as they help suppress gag and laryngeal reflexes, making them ideal for use during anesthesia induction. In fact, many pediatric centers opt to use sevoflurane for inhalation induction to aid in introducing an intravenous line. It's vital to avoid defensive laryngeal reflexes, especially laryngospasm, in this scenario, making it crucial to comprehend these reflexes during light anesthesia in kids. Upon our investigation, we discovered variations in larynx defensive reflexes in kids under propofol or sevoflurane anesthesia. Laryngospasm happened more frequently during sevoflurane anesthesia, while exhalation and coughing reflexes were higher during propofol anesthesia. Such findings indicate that the anesthetic administered can determine how potentially hazardous airway defense reflexes manifest..

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