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ORIGINAL RESEARCH

A Comparison of the Effects of Sevoflurane, Propofol, and Propofol Combined with Butorphanol in Suppressing Sufentanil-Induced cough—A Randomized Controlled Trial

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Objective: To study the safety and efficacy of sevoflurane pretreatment in preventing sufentanil-induced cough in children and to compare its antitussive effect with that of butorphanol, an opioid analgesic that has been proven effective in clinical trials.

Data and Methods: This was a prospective randomized controlled trial. A total of 174 patients who underwent ENT surgery at Chaohu Hospital Affiliated with Anhui Medical University were enrolled and divided into groups S, C and B, with 58 patients in each group, according to the random number table method. General anesthesia was induced with 5% sevoflurane in Group S, 2.5 mg/kg of propofol and 30 μg/kg of butorphanol in Group B, and 2.5 mg/kg of propofol and 1 mL of normal saline in Group C. The cough grade, intraoperative hemodynamic data, blood oxygen saturation, and adverse reactions within 24 h after the operation were recorded.

Results: The overall cough grade significantly differed among the 3 groups ($P<0.05$). Compared with those of Group C, the cough grades of Groups S and B were significantly lower ($P<0.05$). There was no significant difference in the cough grade between Group S and Group B ($P>0.05$). Groups S and B cannot be considered equivalent. There were no significant differences in the MAP, HR, SpO2 or BIS value among the three groups at different time points ($P>0.05$). There was no significant difference in the incidence of postoperative nausea, vomiting, dizziness or chills among the 3 groups ($P>0.05$).

Conclusion: Induction of anesthesia using 5% sevoflurane to reduce Bis to 60 in children significantly reduces the probability of sufentanil-induced coughing (SIC) without significant hemodynamic fluctuations.

Plain Language Summary: When sufentanil is used to induce anesthesia without intervention, there is a high probability of a cough reaction (64.7%), which is the first in a series of complications that can occur during the anesthesia induction period, such as an increased intraocular pressure and an increased intracranial pressure. This condition is called sufentanil-induced coughing (SIC).There are several ways to suppress SIC. However, there are few studies on pediatric SIC, and the drugs most commonly used to prevent SIC require intravenous access establishment; thus, it is not suitable for children. The aim of this study is to investigate the efficacy of sevoflurane, one of the most commonly used anesthetic drugs in children, in preventing SIC.

In this study, the efficacy of sevoflurane in suppressing SIC was compared with that of butorphanol, an opioid analgesic that have been proven effective in clinical trials, by comparing the clinical data of the group of patients who underwent general anesthesia induction with 5% sevoflurane with those of a blank control group. Finally, reducing the BIS value to 60 with 5% sevoflurane effectively prevented SIC while maintaining hemodynamic stability.

Our results can be used as the basis for the increased use of sevoflurane and for further exploration of its efficacy and safety.

Keywords: pediatric surgery, ears, nose, and throat surgery, general anesthesia, sevoflurane, butorphanol

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Introduction

Sufentanil is an opioid analgesic that is widely used in pediatric surgery.[1] Children who undergo general anesthesia induction with sufentanil have better intraoperative hemodynamics, better stability, better postoperative sleep quality, and less postoperative pain.[2] However, studies have shown that the use of sufentanil for induction may lead to severe coughing.[3] This condition is called sufentanil-induced coughing (SIC). The incidence was as high as 64.7% without any intervention.[4] Coughing can lead to a series of complications associated with the induction of anesthesia, such as increased intraocular pressure, increased intracranial pressure, etc, and even emergency tracheal intubation before induction due to severe coughing.[5] Coughing may be caused by the following: (1) sufentanil acting on the μopioid receptor and therefore stimulating the stretch floor reflector and sensory C fibers;[6] (2) sufentanil acting on prebronchial μ opioid receptors and therefore promoting the release of histamine and other substances;[7] (3) sufentanil causing vocal cord stiffness.[8] The use of drug or procedures to prevent SIC is currently the focus of clinical research. Current procedures to prevent coughing include using an infusion pump slowly With sufentanil,[9] perform cough motions in advance,[10] give proper dosing sequence,[11] etc. The drugs used to inhibit choking during the induction of anesthesia include nalbuphine, lidocaine, ketamine, esketamine, magnesium sulfate, dexmedetomidine, remifentanil, and alfentanil[12–15] However, all these drugs require venous access establishment before surgery, and there is no exact dosage for preoperative treatment for children.

Sevoflurane is a commonly used haloether anesthetic. Because of its low blood and tissue solubility, it quickly induces anesthesia, and has a series of advantages, such as a short waking time.[16] During the induction of anesthesia in pediatric patients, the probability of sevoflurane triggering an upper airway reflex is extremely low.[17] Compared with other inhaled anesthetics, it can often lead to a more pleasant induction process in children.[18] In addition, pediatric patients are more likely to cooperate with inhalation anesthesia induction than intravenous anesthesia induction.[19] Sevoflurane is currently one of the most commonly used drugs for inducing anesthesia in pediatric patients. Studies have revealed that, after reaching the clinical concentration, sevoflurane may inhibit the μ receptor through the PKC pathway to inhibit coughing.[20] Sevoflurane reverses the expression of TGF-β1 and VE GF, thus reducing tracheal hyperreactivity.[21] On the basis of these possible principles, no similar clinical studies at home and abroad exist. We plan to study the safety and effectiveness of sevoflurane induction in the prevention of pediatric sufentanil-induced cough. For comparison, we choose propofol, which is commonly used in anesthesia induction and can relax the bronchus and inhibit the airway reflex.[22] In addition, butorphanol is an opioid receptor agonist-antagonist, and many clinical trials have revealed that it has a significant inhibitory effect on SIC.[23] We selected another group that was given butorphanol before induction and induced with propofol to verify the effect of sevoflurane on inhibiting SIC. We aim to introduce a new anesthesia method for pediatric patients.

Materials and Methods

Inclusion and Exclusion Methods

This study was approved by the Ethics Committee of Chaohu Hospital Affiliated with Anhui Medical University (KYXM-202312-0011) and was reviewed by the China Clinical Trial Center (ChiCTR2400086684). Informed consent forms were signed by his or her guardian. This study adhered to the guidelines of the Consolidated Standards of Reporting Trials (CONSORT) and complied with the Declaration of Helsinki.

The inclusion criteria were as follows: (1) underwent ENT surgery (Excluding myringotomy and turbinate reduction). (2) age 4–9 years, ASA I–II. (3) voluntarily joined and signed the informed consent form.

The exclusion criteria were as follows: (1) an allergy to halogenated anesthetics; (2) functional failure of important organs (lung, liver, or kidney); and (3) muscular dystrophy, oropharyngeal obstruction, respiratory infection within in the past two weeks, refused to cooperate, and a history of hemorrhagic disease or coagulation dysfunction. (4) Patients who had received local anesthesia including ear, nose, and throat prior to surgery.

Exit criteria: 1. Laryngeal spasm or severe allergic reactions during anesthesia induction; 2. Perioperative coma or death.

General Information

A total of 174 patients who underwent ear, nose, and throat (ENT) surgery at Chaohu Hospital Affiliated with Anhui Medical University were enrolled in this prospective randomized controlled trial. The patients were divided into Group S, Group C and Group B, with 58 patients in each group, according to a random number table General anesthesia S was induced with 5% sevoflurane in Group S, 2.5 mg/kg of propofol and 30 μg/kg of butorphanol in Group B, and 2.5 mg/kg of propofol and 1 mL of normal saline in Group C. Each grouping scheme was put into an opaque envelope with a code written on the outside of the envelope and handed over to the researcher after sealing. The patients who met the inclusion criteria were given a number. The corresponding numbered envelope was opened, and the intervention was implemented according to the grouping scheme inside the envelope. The treatment regimen for each subject was determined by the generated random sequence.

In our pilot trial (n=15), 53% of patients experienced episodes of coughing after intravenous administration of sufentanil without any intervention, and we hypothesized that pretreatment with sevoflurane would reduce this probability to 25%. With a risk of type I error of 0.05 and an efficacy of 0.9, we decided to recruit 58 people per group, taking into account a 10% loss to follow-up rate.

Methods

Routine examinations were performed after admission. All patients fasted for 6 h and abstained from drinking water for 2 h before surgery. None of the patients used any preoperative medications. Upon arrival to the room, the monitor was connected to monitor HR, SBP, DBP, SpO2 and other vital signs, and the EEG dual-frequency index was measured. All patients were preoxygenated for 2 min. The different groups of drugs used during induction were as follows:

In Group S, the concentration of sevoflurane (Jiangsu Hengrui Pharmaceuticals Co., Ltd) was adjusted to 5% with a volatile tank for prefilling, followed by mask inhalation. When the patient's BIS value dropped to 60, the venous access of the upper limb was opened, and 2.5 μg/kg of sufentanil (Humanwell Healthcare (Group) Co., Ltd.) and 0.6 mg/kg of rocuronium (Jiangsu Hengrui Pharmaceuticals Co., Ltd) were injected intravenously. After the muscles were relaxed for 3 minutes, endotracheal intubation was performed under the guidance of a video laryngoscope.

In Group B, 30 μg/kg of butorphanol (Jiangsu Hengrui Pharmaceuticals Co., Ltd) was given after the upper limb venous access was opened, and, after waiting for 2 minutes, 2.5 mg/kg of propofol (Xi'an Li Bang Pharmaceutical Co., Ltd), 2.5 μg/kg of sufentanil, and 0.6 mg/kg of rocuronium were administered intravenously. After the muscles were relaxed for 3 minutes, endotracheal intubation was performed under the guidance of a video laryngoscope.

In Group C, 1 mL of normal saline was administered after the upper limb venous access was opened, and, 2 minutes after intravenous injection, 2.5 mg/kg of propofol, 2.5 μg/kg of sufentanil and 0.6 mg/kg of rocuronium were given. After the muscles were relaxed for 3 minutes, endotracheal intubation was performed under the guidance of a video laryngoscope.

To avoid experimental errors due to differences in the rate of sufentanil infusion, all infusions of sufentanil were assisted by a micropump at a rate of 2.5 μg/s. From the beginning of the infusion to the end at 2.5 minutes, a researcher used a stethoscope to auscultate the lungs, and if coughing was heard, the duration of coughing and the cough grade were recorded.

During the operation, 6–12 mg/kg of propofol was administered to maintain the BIS value between 45 and 60, 80 μg/kg-1·h-1 of cisatracurium, a muscle relaxant, was administered for maintenance, and 0.05 μg/(kg·min) of remifentanil was administered for maintenance. The infusion speed of propofol and remifentanil was adjusted according to the hemodynamic index and bifrequency index of the brain. After the operation, propofol, cis-atracurium and remifentanil were stopped. All patients received serotonin receptor antagonists 15 minutes before the end of surgery, and postoperative analgesics were not administered to all patients.

Observation Indicators

1. Baseline data: age, BMI, and ASA class.
2. Main therapeutic indices: The frequency of coughing. According to the duration of coughing in the induction period, the grades are as follows: grade 1 (no coughing), grade 2 (coughing time < 3 s), grade 3 (coughing time 3–5 s), and grade 4 (coughing time > 5 s).
3. Secondary outcome measures: 1. Heart rate (HR), SPO2, mean arterial pressure (MAP), and BIS at the following time points: before induction (T1), immediately after intubation (T2), and 1 minute after intubation (T3). 2. Adverse reactions (nausea, vomiting, dizziness, chills) 24 h after surgery.

Statistical Methods

SPSS 26.0 and SAS 9.4 statistical software were used to analyze the data. The Shapiro–Wilk test was used to determine the normality of the data distribution, and the categorical variables were expressed in terms of frequency (scale). Measurement data following or approximately following a normal distribution are expressed as $\bar{x} \pm s$, and an independent sample *t* test was used for comparisons between groups. If the continuous variables were normally distributed, one-way analysis of variance (ANOVA) was performed. Fisher's exact test was performed for categorical variables. The severity of SIC was assessed using Fisher precision tests. For the equivalence test, SAS 9.4 software was used, where the equivalence bound value was (−0.1~0.1), each unilateral α was 0.025, and the 90% confidence interval (CI) of the difference between the unitary value of the lower bound and the population rate of the upper bound was calculated.

Results

Characteristics of the Patients

Of the 191 eligible patients, 174 agreed to participate and were randomly assigned to one of the three groups, with 58 participants in each group. No one was lost to follow-up. There were 58 patients (Figure 1) in each group. The operation

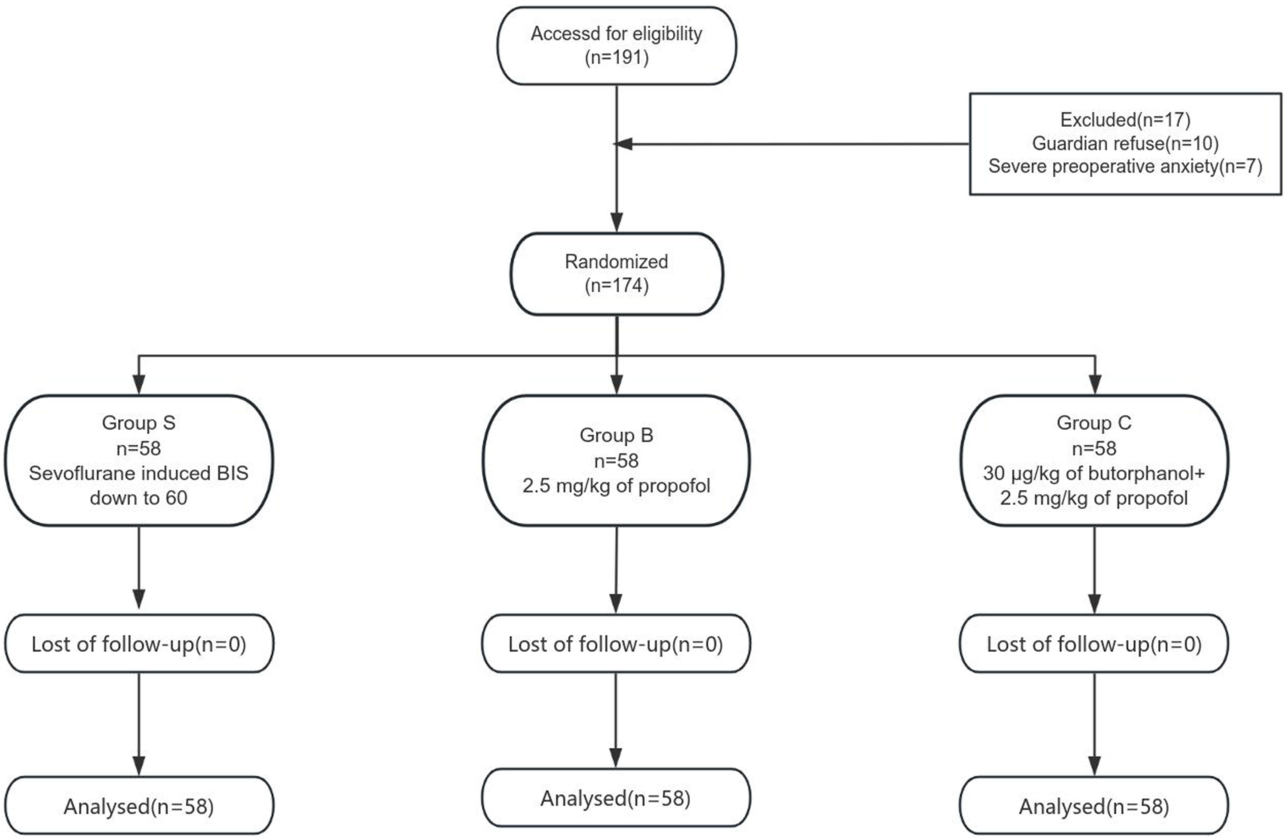

Figure 1 CONSORT diagram of patient recruitment.

Table 1 Comparison of Baseline Data Among the Three Groups (X±s)

	Group S	Group B	Group C	P value
Sex				0.85
Male(n)	28	26	29	–
Female(n)	30	32	29	
Age (years)	6.76±1.62	7.21±1.46	7.06±1.23	0.23
BMI (kg/cm^2)	17.32±2.47	16.96±2.16	17.49±2.32	0.21
ASA (n)				0.86
I	56	55	56	–
II	2	3	2	

was successfully completed in all patients. There were no significant differences in sex, age, BMI or ASA classification between the two groups (P>0.05) (Table 1).

There was a statistically significant difference in the overall cough grade among the 3 groups (P<0.05). Compared with those of Group C, the cough grades of Groups S and B were significantly lower (P<0.05). There was no significant difference in the cough grade between Group S and Group B (P>0.05). Compared with those in Groups S and B, the severity of coughing in Group C was worse (P<0.05) (Table 2).

Pairwise equivalence tests for Groups S, B and C do not indicate that Groups S and B are equivalent (Table 3).

Hemodynamic data (MAP and HR) are shown in Figures 2 and 3. There were no significant differences in the MAP, HR, SpO2 or BIS value among the three groups at different time points (P>0.05) (Table 4).

There was no significant difference in the incidence of postoperative nausea, vomiting, dizziness or chills among the 3 groups (P>0.05) (Table 5).

Discussion

In our study, the probability of choking was 41.3% in the propofol group (Group C), which is lower than that reported in most other related studies. The lower probability of choking may be due to the use of an infusion pump at a lower rate than manual infusion of sufentanil.[9] Propofol is one of the most common sedatives used in anesthesia induction, as it prevents NF-κB activation and effectively reduces airway inflammation by inhibiting the phosphorylation and degradation of I-κBα in lung tissue.[24] Moreover, propofol may cause bronchodilation[22] by reducing the baseline [Ca 2+]i, potentially causing choking. However, it was not effective for SIC inhibition in most related experiments.[12]

Table 2 Comparison of Cough Grade Among the Three Groups

	Group S	Group B	Group C	P value
Level1	49	52	34	–
Level2	2	3	5	–
Level3	6	2	4	–
Level4	1	1	15	–
Number of SIC	9 (15.5%)	6 (10.3%)	24(41.3%)	<0.001

Table 3 Equivalence Test of Cough Grade in the Three Groups

Equivalent Test	Z_L	Z_U	P_L	P_U	Population Rate Difference of 90% CI	Results
S and B group	0.7771	−2.4423	0.2186	0.0073	[−0.1539,0.0505]	not equivalent
S and C group	4.468	1.9762	<0.0001	0.9759	[0.1266,0.3906]	not equivalent
B and C group	5.3968	2.7664	<0.0001	0.9972	[0.1853,0.4354]	not equivalent

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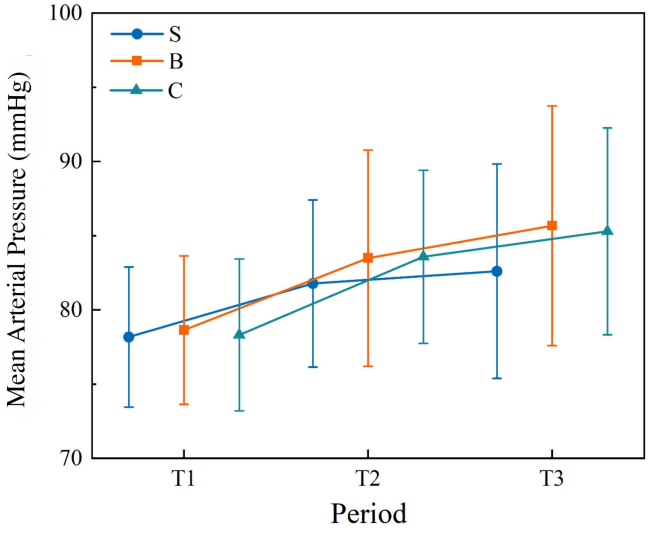

Figure 2 The mean arterial pressure of the three groups at each time.

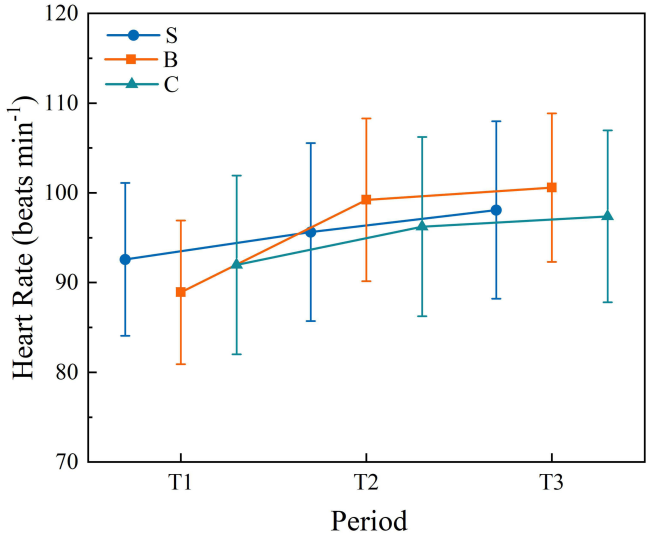

Figure 3 The heart rate of the three groups at each time.

Compared with the normal saline group, the sevoflurane group (Group S) experienced effective suppression of SIC, which may be due to the following three reasons: (1) Sevoflurane inhibits μ receptors during inhalation and thus prevents SIC,[20] which is similar to the findings reported by Xie W et al[4] (2) Sevoflurane reduces tracheal hyperreactivity and thus the incidence of SIC by reversing the regulation of TGF-β1 and VEGF expression. Schutte D[25] et al provided support for this principle. (3) Sevoflurane inhibits SIC by increasing the depth of anesthesia, and this finding warrants further study.

In our study, the probability of choking in the butorphanol (Group B) was similar to that reported in other studies;[26] our experimental results proved that sevoflurane induction is not inferior to butorphanol in inhibiting SIC, and in terms of administration, intravenous access is not needed before sevoflurane administration. For children with severe preoperative anxiety or fear of venous access, sevoflurane is a not only a good choice for anesthesia induction but also a good choice for cough suppression. However, the experimental results do not prove that sevoflurane and butorphanol are equivalent in terms of inhibiting cough during the anesthesia induction period with sufentanil.

Table 4 Comparison of HR, Bis and MAP Before Induction (T1) at the Beginning of Intubation (T2) at the End of Intubation (T3) in the Three Groups (X±s)

Group	Group S	Group B	Group C	P value
MAP(mmHg)				
T1	78.17±4.72	78.64±5.00	78.31±5.12	0.874
T2	81.72±5.64	83.45±7.28	83.59±5.85	0.21
T3	82.60±7.23	85.67±8.07	85.29±6.97	0.056
HR(bpm)				
T1	92.59±8.51	88.91±8.00	91.97±9.97	0.06
T2	95.66±9.94	99.19±9.07	96.33±10.03	0.117
T3	98.10±9.94	100.69±8.32	97.43±9.59	0.141
Bis				
T1	95.45±2.73	94.40±3.01	94.60±3.12	0.131
T2	54.31±8.87	52.72±7.41	55.36±6.84	0.183
T3	51.32±6.70	52.62±6.35	53.29±5.32	0.236
SPO_2(%)				
T1	98.00±0.19	98.07±0.26	98.03±0.18	0.217
T2	97.68±1.12	97.91±1.13	98.07±0.99	0.741
T3	97.38±0.48	97.47±0.50	97.40±0.49	0.612

Table 5 Comparison of Postoperative Adverse Reactions Among the Three Groups

	Group S	Group B	Group C	P value
nausea	3	2	3	
vomiting	0	1	0	
dizziness	2	2	1	
chills	0	1	1	
Total	5(8.6%)	6 (10.3%)	5(8.6%)	0.987

With the advancement of medical technology, the number of pediatric surgeries is also increasing. Studies have shown that up to 50%–70% of children have varying degrees of preoperative anxiety.[27] Preoperative anxiety may lead to more severe pain, which further affects the speed and quality of postoperative recovery and can even lead to a series of postoperative psychological problems.[28] Venous access establishment is a major factor associated with anxiety regarding the induction of anesthesia before surgery.[29] The use of sevoflurane for anesthesia induction allows us to avoid venous access establishment before anesthesia induction and to establish venous access when the child's brain bifrequency index reaches an ideal value, thus effectively avoiding some unnecessary preoperative anxiety factors. In most of the children in Group S, a BIS value of 60 was achieved without the need for venous access establishment, and the subsequent induction process was successful. During the experiment, 3 children in group S showed varying degrees of body motor reactions during the inhalation of sevoflurane, which may be related to the low concentration of sevoflurane inhaled. However, some studies have shown that a 5% sevoflurane concentration has little effect on hemodynamics in children.[30] Moreover, to prevent cough caused by high concentrations of sevoflurane from affecting the experimental results,[31] 5% sevoflurane was finally selected for sedation.

It has been noted that the probability of hypoxemia in pediatric patients undergoing surgery under inhalation induced anesthesia is as high as 5.08%.[32] However, during this experiment, only 1 patient (1.72%) in Group S developed hypoxemia, which may be related to our routine pre-oxygenation technique before surgery. In this experiment, there was no significant difference in the hemodynamic indexes of the three groups of patients during induction.

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Most of the current studies on SIC are related to opioid analgesics, but the adverse reactions caused by opioids in children cannot be ignored, and the opioid analgesics administered to children during the perioperative period may be associated with drug addiction in later stages.[33] At the same time, it may also cause some postoperative adverse reactions, such as nausea, vomiting, dizziness, and so on. The preoperative administration of sevoflurane to suppress SIC can reduce the use of opioid analgesics, which may reduce the probability of surgery-related drug addiction.

There are still some limitations of this study. First, the sample size was small and therefore nonrepresentative of the pediatric ENT surgical population. Second, the corresponding dose range was not set, and multiple groups were established according to the sevoflurane concentration to explore the optimal dose for preventing SIC and determine the dose with the least adverse effects. Third, this study did not involve an evaluation of physiological changes in patients, and the mechanism by which sevoflurane prevents SIC was proposed on the basis of related pharmacology. Moreover, whether the efficacy of sevoflurane in preventing SIC is based on the depth of anesthesia needs further examination. This hypothesis can be further verified by setting up multiple BIS values.

Conclusion

Induction of anesthesia using 5% sevoflurane to reduce Bis to 60 in children significantly reduces the probability of sufentanil-induced coughing (SIC) without significant hemodynamic fluctuations.

Data Sharing Statement

Data supporting the findings of this study are available upon reasonable request from corresponding author Xiaoqiong Xia.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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