Effect of optimizing the induction regimen of drugs in preventing cough reactions in patients undergoing general anesthesia: a single-center, randomized, controlled trial

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Research Article

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Abstract

Background

During the induction of general anesthesia, opioids and endotracheal intubation may cause coughing. This study aimed to determine the safety and clinical effects of an optimized drug induction scheme for general anesthesia to prevent coughing in patients.

Methods

A total of 220 patients aged 18 to 65 years who underwent surgery under general anesthesia with endotracheal intubation were randomly assigned to two groups with 110 cases each; one group was administered with a divided sufentanil bolus (group A) and the other with a single sufentanil bolus (group B). Anesthesia induction was performed according to the drug induction scheme of 0, 1, and 3 min. In group A, intravenous sufentanil was administered at 0.1 µg/kg for 2–3 s; intravenous propofol was administered at 1 min for 20–30 s, rocuronium bromide for 10–15 s, and the remaining sufentanil for 3–5 s after rocuronium bromide administration. In group B, sufentanil was administered intravenously after rocuronium bromide was administered once, and the doses and bolus injection rates of the remaining drugs were the same as those in group A. The primary outcome was a cough reaction caused by opioids. We also recorded the pain associated with drug injection, hemodynamics, and blood oxygen saturation during the induction of general anesthesia.

Results

All patients were included in the statistical analysis. There were 10 cases of sufentanil-induced choking reactions in group A and 0 cases in group B, and the difference was statistically significant ($P < 0.05$). There was no choking reaction of tracheal intubation in the two groups (both $P > 0.05$). There was no severe pain due to propofol and rocuronium injection in the two groups ($P > 0.05$). The mean arterial pressure (MAP), heart rate (HR), and peripheral oxygen saturation ($\text{SpO}_2$) values were within the normal range at each time point during the induction period.

Conclusion

Following the concise general anesthesia induction scheme at 0, 1, and 3 min, an optimized general anesthesia induction regimen of rocuronium bromide that was rapidly administered, and a single final intravenous bolus of sufentanil, sufentanil-induced coughing reaction was completely eliminated.

Trial registration:
**Introduction**

General anesthesia with endotracheal intubation is a commonly used clinical anesthesia technique to establish a stable airway and facilitate airway management. Analgesics such as opioids are used during general anesthesia to suppress the reaction caused by endotracheal intubation. However, opioids often cause a cough response during anesthesia induction [1–3]. Simultaneously, insufficient general anesthesia depth for endotracheal intubation can cause coughing.

The cough response is associated with increased intracranial, intraocular, and intra-abdominal pressures [4]. The choking reaction is unfavorable for patients with high intracranial pressure, aneurysms, and bullae. Once the coughing response is severe, it causes severe fluctuations in circulation, manifested as increased heart rate and elevated blood pressure, with serious consequences that may be life-threatening [5]. The choking reaction during induction of anesthesia in patients with a full stomach can cause reflux of gastric contents and aspiration [6]. Patients infected with the novel coronavirus who have pneumonia experience a cough reaction during anesthesia induction, which can spray secretions or generate aerosols and significantly increase the infection rate of medical staff [7, 8].

Therefore, it is important to optimize the anesthesia dosing regimen to prevent coughing during the induction of general anesthesia. In clinical practice, our team has achieved good results by optimizing the general anesthesia induction drug regimen to reduce the coughing response during the induction period. Therefore, this study aimed to explore the effect of optimizing the general anesthesia induction medication regimen on opioid- and tracheal intubation-induced coughing.

**Materials And Methods**

**Intraoperative and postoperative care**

This study was approved by the Ethics Committee of the First People's Hospital of Pinghu City (ethics number:2020 – 135,10/07/2020), and all patients provided informed consent before they were administered with anesthesia. The study protocol was registered in the Chinese Clinical Trial Registry (http://www.chictr.org.cn) (ChiCTR2200062749; 17/08/2022). The study protocol followed the CONSORT guidelines. The study protocol was performed in the relevant guidelines. The study met the provisions of the Declaration of Helsinki. A total of 220 patients aged 18 to 65 years who underwent surgery under general anesthesia with endotracheal intubation between August 2022 and October 2022 were selected, and the range of motions of their head and neck were within the normal range. The exclusion criteria were as follows: patients with body mass index greater than 30 kg/m²; restricted neck movement; mouth opening < 3 cm; Mallampati grade of 4; poor blood pressure control of ≥ 160/95 mmHg; double-lumen tracheal intubation; asthma, chronic obstructive pulmonary disease, external diseases, airway
hyperresponsiveness, upper respiratory tract infection within the past 2 weeks; or recent use of angiotensin-converting enzyme inhibitors, bronchodilators, and steroid hormones.

Before anesthesia induction, we randomly assigned patients (1:1) using randomized numbers and block randomization (block size of 4) to either the group with divided (group A) or single (group B) bolus of sufentanil.

All patients routinely fasted for 6–8 h and abstained from drinking for 2 h before the induction of anesthesia. None of the patients had received preoperative drugs prior to anesthesia. After entering the operating room, the patient was placed in a supine position, an upper extremity vein was established, and 7–8 ml/kg Ringer’s solution was infused before induction of anesthesia. The patient’s blood pressure, pulse oximetry, electrocardiogram, and heart rate were continuously monitored using a multifunction monitor (GE Healthcare). The baseline value was obtained 5–10 min after the patient entered the operating room.

General anesthesia with endotracheal intubation was administered. Three minutes before the induction of anesthesia, oxygen inhalation at a flow rate of 5–6 L/min was administered with a pressurized mask; then, general anesthesia was induced. Drugs for general anesthesia induction included midazolam (0.04–0.05 mg/kg), lidocaine (1 mg/kg), propofol (1.5–2 mg/kg), rocuronium (0.8 mg/kg; diluted to 2 mg/ml), sufentanil (0.4–0.5 µg/kg; diluted to 5 µg/ml). Anesthesia induction was performed according to the drug induction schedule of 0, 1, and 3 min. In group A, intravenous midazolam was administered at 0 min for 3–5 s, lidocaine for 3–5 s, and sufentanil at 0.1 µg/kg for 2–3 s; intravenous propofol was administered at 1 min for 20–30 s, rocuronium bromide for 10–15 s, and the remaining sufentanil for 3–5 s; the total time was controlled within 2 min. In group B, the complete dose of sufentanil was administered intravenously after rocuronium bromide was administered once, and the doses and bolus injection rates of the remaining drugs were the same as those in group A (Fig. 1).

After propofol was administered, the patient should fall asleep, and the mandible was lifted to open the airway. When the rocuronium bromide bolus was completed and a muscle relaxation effect was produced, breathing was manually or machine-controlled, and the airway pressure was controlled to below 15 cmH$_2$O. After 1 min of intravenous injection of general anesthesia induction drugs, endotracheal intubation was performed and connected to an anesthesia machine to control breathing. The set tidal volume was 7–8 ml/kg, respiratory rate was 12–14 times/min, and the tidal volume and respiratory rate were adjusted as needed to maintain a carbon dioxide partial pressure of 35–45 mmHg.

The type of endotracheal tube is generally 7.0# or 7.5# for men and 6.5# or 7.0# for women.

**Outcome measurements**

The primary outcome of the current study was a cough reaction caused by opioids. We recorded the choking reaction caused by opioid administration and tracheal intubation, injection pain and pain level of both propofol and rocuronium bromide, hemodynamics, and blood oxygen saturation during the induction of general anesthesia. At the same time, the time from propofol injection to completion of
tracheal intubation, the time from induction to completion of tracheal intubation, glottis exposure time, tracheal intubation time, intubation conditions, and degree of glottis exposure were also recorded. The patient's tracheal intubation comfort was evaluated after recovery. The evaluation of patient comfort on endotracheal intubation after recovery from general anesthesia was also recorded.

The physical characteristics of the patients, including sex, age, height, weight, body mass index, and Mallampati classification, were recorded. The degrees of choking reaction were as follows: no cough (0 times), mild cough (1–2 times), moderate cough (3–5 times), and severe cough (>5 times) [9]. The degrees of pain from propofol injection were classified into the following: Grade I (no pain), the patient did not report pain and no changes in expression or body movement were observed; Grade II (mild pain), the patient reported mild pain with or without changes in expression, or slight shaking of the forearm; Grade III (moderate pain), the patient reported pain accompanied by obvious changes in expression, or arm retraction or lifting; Grade IV (severe pain), the patient reported intense pain, accompanied by shouting, extreme pain in facial expressions, forceful arm retraction or lifting, tears, and the like. Rocuronium injection pain was divided into four grades: Grade I, no upper limb movement; Grade II, slight shaking of the forearm; Grade III, obvious shaking of the forearm; and Grade IV, lifting the forearm or upper limb struggle. For the intubation conditions, Cooper's score was used to evaluate the position of the glottis, cough reflex, and difficulty of laryngoscope insertion as excellent, good, fair, and poor. Glottis exposure: The Cormack-Lehane grading method was used to observe glottis exposure during tracheal intubation. The hemodynamics and blood oxygen saturation during the induction of general anesthesia were measured at several time points: 5–10 min after entering the room (T0), after anesthesia administration and before intubation (T1), immediately after tracheal intubation (T2), 1 min after tracheal intubation (T3), 3 min after tracheal intubation (T4), and 5 min after tracheal intubation (T5).

Sample size calculation

The sample size of the present study was calculated using PASS version 15.0 (NCSS, LLC., Kaysville, UT, USA). According to a pilot study (unpublished data), the primary outcome of opioid-induced cough response in group A was 10% and that in group B was 0%. Based on the pilot study, a sample size of 190 patients was needed to provide a power of 0.9 and a significance of 0.05. Considering a 15% probability of dropout, 220 patients were recruited for this study.

Statistical analysis

Analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Continuous data were verified and distributed using the Shapiro–Wilk test. Normally distributed data were represented as mean ± standard deviation, and non-normally distributed data were expressed as median (interquartile range). Normally distributed data were analyzed using an independent sample t-test to compare the differences between the groups in terms of outcome parameters. Non-normally distributed data were tested using the Mann–Whitney U test to analyze statistical differences between the groups. For intragroup comparisons, paired t-tests were used to examine differences in the mean arterial pressure (MAP) and heart rate (HR)
from the baseline values at each time point. The chi-square test or Fisher's exact test was used to compare differences in counting data. Statistical significance was set at $P<0.05$.

**Results**

All patients completed the study (Fig. 2). There were no significant differences in the baseline indicators between the two groups, including age, body mass, body mass index, male-to-female ratio, American Society of Anesthesiologists (ASA) classification, and Mallampati classification (all $P>0.05$), as shown in Table 1.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Group A</th>
<th>Group B</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.8 ± 10.6</td>
<td>48.2 ± 12.1</td>
<td>0.750</td>
</tr>
<tr>
<td>Gender (male / female)</td>
<td>58/52</td>
<td>61/49</td>
<td>0.686</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62.3 ± 11.9</td>
<td>64.7 ± 10.2</td>
<td>0.766</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164.2 ± 8.7</td>
<td>163.8 ± 7.7</td>
<td>0.699</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>23.7 ± 2.9</td>
<td>24.0 ± 2.8</td>
<td>0.333</td>
</tr>
<tr>
<td>ASA class I /II</td>
<td>6/104</td>
<td>9/101</td>
<td>0.425</td>
</tr>
<tr>
<td>Mallampati grade ( / / / )</td>
<td>37/69/4</td>
<td>40/65/5</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

NOTE: Data are presented as mean ± standard deviation and number of patients (frequency); Abbreviations: BMI, Body Mass Index; ASA, American Society of Anesthesiologists

In groups A and B, 10 cases and 0 cases of choking reactions occurred during the pre-injection of low-dose sufentanil, respectively, and the difference between the two groups was statistically significant ($P<0.05$). No choking reaction occurred with administration of the remaining dose of sufentanil or tracheal intubation in the two groups (both $P>0.05$). There was no severe pain in patients with propofol and rocuronium injection in the two groups (both $P>0.05$), and there was no significant difference between the two groups in terms of the degree of glottis exposure and the classification of intubation conditions (both $P>0.05$), as shown in Table 2.
Table 2
Comparison of sufentanil and intubation induced cough response between the two groups (n = 110)

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufentanil induced cough reaction, n(%)</td>
<td>10</td>
<td>0</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Cough degree (///)</td>
<td>100/3/4/3</td>
<td>110/0/0/0</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Intubation induced cough reaction, n(%)</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Propofol injection pain (///)</td>
<td>105/4/1/0</td>
<td>90/16/4/0</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Rocuronium injection pain (///)</td>
<td>97/7/6/0</td>
<td>88/12/10/0</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>C-L grade (///)</td>
<td>106/4/0/0</td>
<td>107/3/0/0</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Intubation condition (///)</td>
<td>92/18/0/0</td>
<td>101/9/0/0</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

NOTE: Data are presented as number of patients (frequency);

The glottis exposure time of groups A and B was 10.0 ± 1.1 s and 10.5 ± 4.3 s, respectively. The intubation time was 20.5 ± 4.8 s and 20.9 ± 5.2 s, the time from induction to completion of tracheal intubation was 200.5 ± 4.8 s and 200.9 ± 5.2 s, and the time from propofol injection to completion of tracheal intubation was 140.5 ± 4.8 s and 140.9 ± 5.2 s for groups A and B, respectively. There was no significant difference between groups (all P > 0.05), as shown in Table 3.

Table 3
Time index of endotracheal intubation in two groups (n = 110)

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of glottic exposure (s)</td>
<td>10.0 ± 1.1</td>
<td>10.5 ± 4.3</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Duration of endotracheal intubation (s)</td>
<td>20.5 ± 4.8</td>
<td>20.9 ± 5.2</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Duration from the beginning of general anesthesia induction to the completion of endotracheal intubation (s)</td>
<td>200.5 ± 4.8</td>
<td>200.9 ± 5.2</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Duration from the beginning of propofol injection to the completion of endotracheal intubation (s)</td>
<td>140.5 ± 4.8</td>
<td>140.9 ± 5.2</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

NOTE: Data are presented as mean ± standard deviation;
There was no significant difference in MAP, HR, and SpO\textsubscript{2} between the two groups at each time point during the induction period (all $P > 0.05$). The values of MAP, HR, and SpO\textsubscript{2} were within the normal range at each time point during the induction period.

The parameters were also compared within each group. In group A, the MAP values were significantly lower at T1–T5 than at T0 ($P < 0.05$ or $P < 0.01$); in group B, the MAP values were significantly lower at T1 and T3–T5 (all $P < 0.01$), as shown in Fig. 3. In group A, the HR values were significantly increased at T1–T4 than at T0 ($P < 0.05$ or $P < 0.01$), and in group B, the HR values were significantly lower at T1–T4 (all $P < 0.01$), as shown in Fig. 4.

After awakening from the anesthesia, the patients in the two groups were asked whether they experienced any discomfort such as pain during the induction period. They all indicated that they had no discomfort, and the difference was not statistically significant ($P > 0.05$).

**Discussion**

Following the concise general anesthesia induction steps of 0, 1, and 3 mins, an optimized general anesthesia induction regimen of rocuronium bromide that was administered rapidly, and a single final intravenous bolus of sufentanil, sufentanil-induced coughing reaction was completely eliminated. The hemodynamic indices were also stable during the induction period of general anesthesia, and the patients did not experience any particular discomfort.

The primary objective of this study was to investigate the preventive effect of opioid-induced coughing. Therefore, in the order of administration, we fully considered the time of onset and effects of lidocaine, propofol, and rocuronium bromide on cough suppression. In terms of study design, midazolam and lidocaine were administered intravenously in sequence at 0 min; propofol, rocuronium, and sufentanil were injected sequentially at 1 min and within 50–60 seconds; 1 min after this administration, the drugs for anesthesia induction reached their peak effect, while ensuring that the patients did not choke and had relatively stable hemodynamics during general anesthesia induction of tracheal intubation. At the same time, among the induction drugs, lidocaine has the best effect on preventing opioid cough and suppressing emergency response to endotracheal intubation [10–12]. Injection of propofol before rocuronium can avoid pain caused by rocuronium injection when the patient is awake; moreover, the injection pain caused by rocuronium bromide is more severe than that of propofol [13, 14]. Therefore, the preferential intravenous injection of propofol can cause the patient to sleep while taking advantage of the analgesic effect of lidocaine [4, 15], and when combined with diluted rocuronium bromide, this can ultimately reduce or avoid the pain of rocuronium bromide injection.

Opioids such as sufentanil can attenuate or eliminate the stress response caused by endotracheal intubation, allowing patients to tolerate the procedure without coughing. However, in a single intravenous injection of fentanyl or sufentanil, up to 65% of patients will have brief coughs [2]. Many clinical studies have been conducted on the prevention of choking reactions to fentanyl or sufentanil. The methods to
prevent opioid choking include central administration [16], active deep breathing during the induction period, divided administration [9], lowering the injection speed [9], changing the injection sequence, and pre-injecting dexamethasone, lidocaine [10, 11, 17], dexmedetomidine [18, 19], propofol [20, 21], dezocine [22], rocuronium bromide, and other drugs [23]. In this study, pre-injection of sufentanil at 0.1 µg/kg before propofol resulted in a 9% incidence of choking reactions. Although slowing down the injection speed, dividing the bolus injection, or using other drugs for prevention can reduce the incidence and degree of choking, it cannot be completely avoided nor independently controlled. However, no choking reaction occurred during the last single intravenous bolus injection of sufentanil, mainly because previous intravenous bolus injections of lidocaine, propofol, and rocuronium bromide effectively played a role in suppressing the opioid choking reaction effect.

Both propofol and rocuronium, especially rocuronium, can cause injection pain [23–25]. Our observations showed that there was no severe injection pain during intravenous propofol and rocuronium administration in either group and no facial expressions of pain during rocuronium injection. The main reason for this is the effect of lidocaine and propofol before rocuronium injection, and the effective dilution of rocuronium bromide. The program considers the characteristics of avoiding drug choking and coughing, minimizing or avoiding drug injection pain, and faster onset of drug effects; it can improve the comfort and satisfaction of patients in medical treatment.

Reflux aspiration during induction in satiated patients did not occur in this study because of the elective surgery. A general anesthesia induction program should be reasonably formulated for patients with a full stomach, which can effectively prevent coughing during the induction period and complete tracheal intubation quickly, as well as effectively prevent reflux and aspiration in patients with a full stomach [26].

This study had some limitations. First, this study was a single-center study, and no multi-center larger sample observation was conducted. Second, this study only reported on observations during the induction period and not the entire perioperative period. Third, this study only used sufentanil and other opioid induction regimens requiring further in-depth research. Fourth, this study failed to achieve investigator blinding due to the method of administration.

**Conclusion**

In conclusion, following the concise general anesthesia induction steps of 0, 1, and 3 min, an optimized general anesthesia induction drug regimen of rocuronium bromide that was rapidly administered, and a single final intravenous bolus of sufentanil, sufentanil-induced coughing reaction was completely eliminated. The hemodynamic indices were stable during the induction period of general anesthesia, and the patients had no particular discomforts.

**Abbreviations**

MAP
Mean arterial pressure
HR
Heart rate
SpO\textsubscript{2}
Peripheral oxygen saturation
ASA
American Society of Anesthesiologists

**Declarations**

**Ethics approval and consent to participate**

This study was conducted in strict compliance with medical ethics and approved by the Ethics Committee of the First People's Hospital of Pinghu City (ethics number 2020-135. Informed consent was obtained from all the patients.

**Authors' contributions**

Lei Wang and Xing Lu contributed to the study conception and design. Material preparation, data collection, and data analysis were performed by Yi Cheng, Youchuan Zhang, DeXiang Zhao and Yanhong Zhu. The first draft of the manuscript was written by Lei Wang, and all authors commented on previous versions of the manuscript. All authors have read and approved the final manuscript.

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**Competing interests**

The authors declare that they have no competing interests.

**Consent for publication**

Consent for publication was obtained from all participants.

**Availability of data and materials**

The datasets used and analyzed in the current study are available from Lei Wang, the corresponding author, upon reasonable request (13615739338@163.com).
References


Figures
Figure 1

Schematic diagram of the induction of general anesthesia in the two groups.
Figure 2

The flowchart of the study.
Figure 3

The comparison of the mean arterial pressure between the two groups during induction of general anesthesia.
Figure 4

The comparison of the heart rates between two groups during induction of general anesthesia.