Research Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2023.52.008185

The Impact of Different Dosages of Oxycodone on the Incidence of Cough Reflex During Target-Controlled Infusion of Remifentanil: A Single-Center Randomized Controlled Clinical Trial

Huidang Ouyang, Shaoquan Jiang, Wenlong Lu, Zhiming Zhang and Lingkun Huang*

Department of Anesthesiology, The First People's Hospital of Chenzhou, China

***Corresponding author:** Lingkun Huang, Department of Anesthesiology, The First People's Hospital of Chenzhou, Chenzhou City, Hunan Province, 423000, China

ARTICLE INFO

Received: June 03, 2023

Published: August 15, 2023

Citation: Huidang Ouyang, Shaoquan Jiang, Wenlong Lu, Zhiming Zhang and Lingkun Huang. The Impact of Different Dosages of Oxycodone on the Incidence of Cough Reflex During Target-Controlled Infusion of Remifentanil: A Single-Center Randomized Controlled Clinical Trial. Biomed J Sci & Tech Res 52(1)-2023. BJSTR. MS.ID.008185.

ABSTRACT

Objective: The aim of this study was to investigate the effect of different doses of oxycodone on preventing cough reflex induced by remifentanil target-controlled infusion (TCI).

Methods: A total of 120 patients scheduled for elective gynecological surgery under general anesthesia were selected. The patients were randomly divided into four groups (n=30): control group (group C) received intravenous normal saline 10ml within 1 minute before anesthesia induction, oxycodone injection groups consisted of group O1, group O2, and group O3 received intravenous oxycodone at doses of 0.03mg/kg, 0.07mg/kg, and 0.1mg/kg, respectively. Five minutes later, remifentanil TCI was initiated at a target effect-site concentration of 4ng/ml, and the occurrence of cough reflex within 1 minute after remifentanil administration was recorded. Mean arterial pressure (MAP), heart rate (HR), and oxygen saturation were recorded at baseline (T0), at the end of oxycodone injection (T1), before intubation (T2), and 1 minute after intubation (T3). Adverse events during the observation period were also recorded.

Results: Compared with the control group, the incidence of remifentanil-induced cough was significantly reduced in the O1, O2, and Group Q3s (P<0.001, P=0.001, P<0.001, respectively). Compared with the Group Q1, the incidence of remifentanil-induced cough was significantly lower in the Group O2 (P=0.002). There was no statistical difference in the incidence of remifentanil-induced cough between the O2 and Group Q3s (P>0.05). There was no statistically significant difference in the incidence of hypotension and severe bradycardia among the groups (P=0.951, P=0.054).

Conclusion: Oxycodone at doses of 0.07mg/kg and 0.1mg/kg effectively suppresses remifentanil-induced cough during TCI. A dose of 0.07mg/kg oxycodone completely inhibits remifentanil-induced cough during TCI and demonstrates a better effect than doses of 0.03mg/kg and 0.1mg/kg oxycodone in suppressing remifentanil-induced cough, with no significant difference compared to the effect of 0.07mg/kg oxycodone.

Keywords: Remifentanil; Target-Controlled Infusion; Cough; Oxycodone

Abbreviations: TCI: Target-Controlled Infusion; MAP: Mean Arterial Pressure; CR: cough reflex; RIC: Remifentanil-Induced Cough; HR: heart rate; IOC: Index of Consciousness

Introduction

Currently, remifentanil, as a novel and ultra-short-acting analgesic, is widely used in special patient populations such as children, the elderly, pregnant women, and obese patients. Its unique pharmacological characteristics make it more suitable for target-controlled infusion during anesthesia induction and maintenance, it is commonly used in conjunction with other medications for anesthesia induction or maintenance. However, it is also frequently used alone for sedation during clinical invasive procedures [1,2]. However, during the process of general anesthesia induction, if remifentanil is chosen as

the target-controlled infusion drug, partial patients may experience cough reflex (CR), with an incidence rate of 26-54% [3,4]. CR can cause patient discomfort, increase the risk of trauma and bleeding, as well as elevate intrathoracic pressure, intracranial pressure, and intra-abdominal pressure, leading to circulatory changes such as blood pressure fluctuations and arrhythmias. Severe coughing can potentially induce coronary ischemia and laryngeal and bronchial spasms. Caution should be exercised in managing the occurrence of cough reflex in patients undergoing neurosurgery, vascular surgery, and ophthalmic surgery. Currently, clinical studies have been conducted on the prophylactic effect of pre-injection Oxycodone on fentanyl and sufent anil-induced cough reflex [5]. However, there have been no reports on clinical trial studies investigating the effects of oxycodone on TCI remifentanil-induced cough reflex. Therefore, this study aims to investigate the influence of pre-injection oxycodone on CR through a clinical randomized controlled trial, providing reference for clinical application.

Materials and Methods

General Information

A total of 120 patients planned for elective gynecological surgery from August 2022 to May 2023 at the First People's Hospital of Chenzhou were selected for this study. The patients were classified into ASA grades I-II and aged between 18 to 65 years old. This study has been approved by the Ethics Committee of the First People's Hospital of Chenzhou City (2022018H), and informed consent has been obtained from all enrolled gynecological patients. Using a random number table method, the patients were divided into a control group (Group C) and different doses of oxycodone groups (Groups O1, O2, and O3), with 30 cases in each group.

Exclusion Criteria Included:

(1) Previous respiratory system diseases such as bronchial asthma, chronic cough, chronic bronchitis, bronchiectasis, COPD, etc.; and a history of upper respiratory tract infection within the prior two weeks;

(2) Severe cardiac, hepatic, or renal dysfunction;

(3) Allergy or abuse history of opioid drugs;

(4) Body weight lower or higher than 20% of the standard weight;

(5) Long-term use of ACE inhibitors, bronchodilators, corticosteroids, and other medications.

Methods

No pre-medication was administered to the patients before surgery. After the patient entered the operating room, an 18-gauge cannula needle was inserted in the left forearm for intravenous access, and lactated Ringer's injection (8 ml/kg/h) was infused. Routine monitoring included electrocardiography (ECG), pulse oximetry (SpO2), mean arterial pressure (MAP), heart rate (HR), and the measurement of the index of consciousness (IOC). Before anesthesia induction, the control group received 10 ml of normal saline intravenously. Group O1, O2, and O3 received intravenous injections of oxycodone (Enhua, Xuzhou, Jiangsu,China) at doses of 0.03 mg/kg, 0.07 mg/kg, and 0.1 mg/kg, respectively. Five minutes later, target-controlled infusion with an effect-site concentration of remifentanil (Renfu, Yichang, Hubei, China) at 4 ng/ml was initiated, and the occurrence of cough reflex within 1 minute after remifentanil administration was recorded for each group. Subsequently, midazolam 0.05 mg/kg and cisatracurium 0.15 mg/kg were intravenously administered, followed by Remimazolam 0.2 mg/kg, and endotracheal intubation was performed. After successful intubation, PETCO2 was connected to maintain it within the normal range(35mmHg-45mmHg). This clinical trail was conducted with the participation of two anesthesiologists. One was responsible for preparing the experimental drugs, operating the target-controlled infusion pump for remifentanil, and administering the experimental drugs according to the assigned group. The other was a senior anesthesiologist with more than 5 years of experience in anesthesia practice, responsible for completing endotracheal intubation, recording the occurrence time and frequency of cough reflex during induction, vital signs at key time points, and adverse events. The administering anesthesiologist was unaware of the experimental group when recording the cough reflex responses.

Observational Indicators

(1) The occurrence time and frequency of cough reflex during induction were recorded, as well as the predicted plasma concentration and effect-site concentration of remifentanil at the time of cough reflex. Cough reflex severity was categorized as follows: no cough (0 times), mild cough (1-2 times), moderate cough (3-4 times), severe cough (≥5 times).

(2) Blood pressure, heart rate, oxygen saturation, and IOC values were recorded at T0, T1, T2, and T3.

(3) The occurrence of adverse events such as respiratory depression, muscle rigidity, bradycardia, hypotension, hypoxemia, nausea and vomiting, and shivering were documented.

Statistical Analysis

Statistical analysis was performed using SPSS 19.0 software. Descriptive statistics were expressed as mean ± standard deviation for normally distributed data with homogeneous variance, and as median (Q25, Q75) for non-normally distributed data. One-way analysis of variance (ANOVA) was used for intergroup comparisons, followed by appropriate testing methods for pairwise comparisons. The chi-square test or Fisher's exact test was used for statistical analysis of count data. A significance level of $P < 0.05$ was considered statistically significant.

General Demographic Comparison

This study recruited 153 patients, of which 120 patients met the inclusion criteria and were enrolled, while 33 patients were not included in the study due to not meeting the criteria. The remaining 120 patients were randomly assigned to four groups. All patients successfully completed the relevant clinical procedures and treatments. After the expected clinical data reached the predetermined standards, statistical analysis was conducted. The flowchart of the study is shown in Figure 1. There were no significant differences in age, weight, height, and ASA classification among the four groups (Group C, Group Q1, Group O2, and Group Q3) in terms of general demographics (see Table 1).

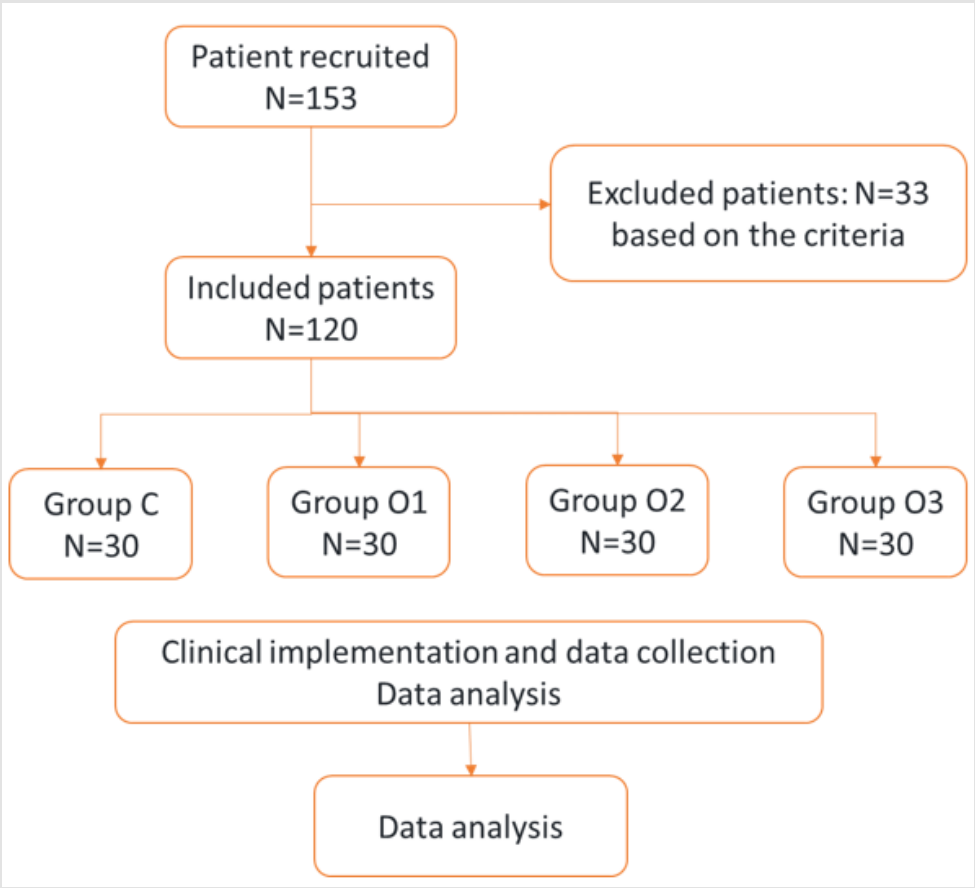

Figure 1: The research Flowchart.

Table 1: Comparison of general demographics among groups.

Group	N	Age(years)	Weight(kg)	Height(cm)	ASA(I/II)
C	30	50±10	68±6	159±8	16/14
O1	30	50±10	71±7	158±7	16/14
O2	30	50±9	69±8	161±4	17/12
O3	30	48±8	69±9	159±6	14/16

Comparison of Adverse Events Occurrence

The incidence of hypotension in the four groups was 3.3%, 3.3%, 3.3%, and 6.7%, respectively, with no significant difference between the groups (P=0.951). No severe bradycardia events occurred in any of the four groups (see Table 2). Patients who experienced hypotension and bradycardia were promptly treated with intravenous administration of dopamine and atropine, resulting in rapid normalization. The number of cases with muscle rigidity were 2, 3, 3, and 1 for Group C, Group Q1, Group O2, and Group Q3, respectively (Table 3). One case of hypoxemia occurred in Group O2, and two cases occurred in Group Q3; no other groups had cases of hypoxemia. Patients with hypoxemia

were managed with high-flow oxygen supplementation via a mask, leading to restoration of normal SpO2 levels (Table 4). None of the four groups experienced adverse reactions such as nausea, vomiting, or shivering.

Table 2: Comparison of adverse events among groups.

Group	N	Hypotension incidence (%)	Severe bradycardia (%)
C	30	1 (3.3%)	0 (0%)
O1	30	1 (3.3%)	0 (0%)
O2	30	1 (3..3%)	0 (0%)
O3	30	2 (6.7%)	0 (0%)

Table 3: Comparison of cough incidence and severity among groups.

Group	N	Cough incidence %	Cough severity		
			Mild	Moderate	Severe
C	30	30	3	4	2
O1	30	16.67*	2	3	0
O2	30	6.67	1	1	0
O3	30	3.33	0	1	0

Note: *Cmpared with Group C and Group O2, O3 P<0.05.

Table 4: Comparison of MAP and HR at different time points among groups.

	Group	T0	T1	T2	T3
MAP	C	87.2±11.3	84.5±10.4	83.2±10.6	85.3±11.5
	O1	88.3±12.2	86.3±11.0	85.4±9.5	87.6±9.7
	O2	85.4±12.7	84.6±11.7	83.9±10.5	85.9±9.4
	O3	86.5±11.4	83.7±11.2	83.1±10.6	84.5±10.1
HR	C	75.4±8.3	74.6±6.7	73.9±7.3	76.7±9.2
	O1	76.5±10.2	75.8±7.2	74.5±9.8	75.3±6.5
	O2	74.9±8.9	73.6±7.9	74.0±8.4	75.6±7.3
	O3	75.7±9.2	74.5±7.5	73.9±8.6	74.3±6.8

Discussion

Remifentanil is a commonly used anesthetic analgesic drug in clinical practice. According to foreign studies, the incidence of cough reflex induced by remifentanil is 25-34% when the target concentration in the effect-site during the induction of general anesthesia is 4 ng/ml [6,7]. The control group in this study had an incidence rate of 30%, which is similar to previous research results. Remifentanil has the advantages of fast onset, rapid distribution, short elimination half-life, and quick postoperative recovery. Compared to fentanyl and sufentanil, remifentanil can more effectively suppress the stimulation response caused by tracheal intubation during the induction of general anesthesia while maintaining hemodynamic stability [8]. Therefore, remifentanil is considered an ideal ultra-short-acting anesthetic analgesic [9]. During TCI with remifentanil using the Minto model, the maximum infusion rate allowed is 1200 ml/h, and the highest plasma concentration allowed is 50 ng/ml. Remifentanil acts on the central nervous system. The equilibrium half-life between plasma concentration and effect-site concentration is 1.0-1.5 minutes [10]. Although the target-controlled plasma concentration is not ideal, and the effect-site concentration is more strongly correlated with the depth of anesthesia, using target-controlled effect-site concentration may lead to sudden increase in plasma concentration, which is more likely to cause significant fluctuations in blood drug concentration and thus induce cough reflex because the target-controlled effect-site concentration does not limit the peak value of plasma concentration.

Cough reflex and pain conduction share similarities in the involvement of glutamate, substance P, NMDA receptors, NK1 receptors, μ-opioid receptors, and δ-opioid receptors [11]. Studies have shown that compared to equipotent doses of fentanyl, sufentanil, and alfentanil, remifentanil has a higher incidence and severity of cough reflex [3,12]. The specific mechanism of remifentanil-induced cough reflex is still uncertain and there are several hypotheses [13,14]:

1) Activation of pre-ganglionic μ receptors by opioid drugs leads to the release of histamine and neuropeptides from sensory fiber terminals, resulting in cough reflex and bronchial constriction [15]. Opioid receptors in the central nervous system are closely associated with the occurrence and regulation of cough reflex.

2) Opioids may inhibit the transmission of sympathetic impulses in the central nervous system while activating the parasympathetic nervous system, causing reflex bronchoconstriction and cough.

3) Opioids can cause sudden glottic closure and stiffness of chest and abdominal muscles, leading to upper airway soft tissue obstruction, which can also explain the induction of cough by opioids.

4) Chemoreceptors in the lungs, such as irritant receptors and vagal C-fiber receptors, are involved in the process of coughing.

5) Remifentanil formulations contain glycine components.

Research experiments have found that the administration of 1 mg of glycine can stimulate the chemoreceptors in the tracheal mucosa, leading to a cough reflex [16]. Furthermore, remifentanil can activate NMDA receptors, whereas fentanyl and sufentanil cannot. Multi-center studies have shown that compared to fentanyl, remifentanil has a higher incidence of muscle rigidity [17], which is one of the mechanisms underlying opioid-induced coughing. Coughing during the induction of general anesthesia can cause significant hemodynamic fluctuations, posing risks for patients with high intracranial pressure, elevated intraocular pressure, and pulmonary bullae [6]. The occurrence of Remifentanil-Induced Cough (RIC) is influenced by factors such as dosage, administration route, age, gender, and smoking [18,19], thus this study selected female patients to exclude the influ-

ence of gender on remifentanil-induced cough [19]. A uniform dosage was administered via upper limb intravenous injection. When the plasma concentration exceeds the effect-site concentration, patients are more prone to coughing. Coughing does not occur when the difference between plasma and effect-site concentrations is reduced or in a steady-state condition [4]. Moreover, efforts were made to minimize the influence of other factors. Literature shows that RIC typically occurs within 1 minute after remifentanil administration, hence the observation period was set at 1-minute post-administration. Oxycodone is a semi-synthetic opioid analgesic derived from the opium alkaloid thebaine.

It is a dual agonist of the μ-opioid receptor and the κ-opioid receptor and primarily acts on the presynaptic membrane of neurons in the central nervous system to reduce or block the transmission of C fibers to spinal dorsal horn neurons, thereby providing analgesia. However, its affinity for the μ-opioid receptor is much lower than that of morphine. Additionally, it can act on κ-opioid receptors, exerting analgesic effects on organs composed of smooth muscle. Its actions mainly focus on the central nervous system and smooth muscles, providing sedative, analgesic, and antitussive effects. Research by Tang Zuolei et al. demonstrated that preoperative intravenous administration of oxycodone significantly suppressed fentanyl-induced coughing [10] and also save the dosage of propofol in flexible bronchoscopy [20], but the exact mechanism of action remains unclear and may involve:

1) direct action of oxycodone on the cough center in the medulla oblongata to suppress RIC [21].

2) competitive inhibition of fentanyl binding to the μ-opioid receptor by oxycodone and activation of the κ-opioid receptor to antagonize the stimulatory effect of fentanyl on the μ-opioid receptor [22].

In this trail, the incidence of coughing in groups C, O1, O2, and O3 was 30%, 16%, 6.67%, and 3.33%, respectively; the incidence of moderate or severe RIC was 16.7%, 6.67%, 3.33%, and 0.

These results indicate that preoperative administration of high-dose oxycodone can effectively suppress CR. This suggests a synergistic effect between oxycodone and remifentanil in inhibiting tracheal intubation response, with dose dependency. Group O3, which received a combination of oxycodone and remifentanil, showed a trend of decreased blood pressure and heart rate.

Possible Reasons Include

1) In this study, remifentanil at a target-controlled infusion (TCI) concentration of 4 ng/ml was already effective in suppressing the stress response during tracheal intubation;

2) The ratio of equipotent doses between oxycodone and remifentanil is 1:100[23], indicating that high-dose oxycodone may not be favorable for maintaining hemodynamic stability during the induction of anesthesia.

Limitations

This was a single center randomized controlled study with a small number of cases observed clinically, and the observed indicators were relatively limited, without the ability to compare more indicators during the induction period of general anesthesia. Although three different doses of oxycodone were used in this study, finding a better dose-response relationship would require more detailed subgroups, such as grouping based on time intervals. Additionally, gradually increasing the low target concentration infusion of remifentanil itself can reduce the occurrence of coughing, suggesting that pretreatment infusion of oxycodone may not be necessary for low target concentrations of remifentanil. In conclusion, pre-administration of intermediate-dose oxycodone 5 minutes in advance significantly inhibits remifentanil-induced coughing. This method not only improves anesthesia safety but also effectively avoids the serious complications caused by RIC during the induction period of anesthesia.

Acknowledgments

We would like to express our gratitude to the operating room nurses for establishing smooth intravenous access during the course of this study and for their cooperation in facilitating the successful implementation of the research.

Funding Support

This study was supported by the following funding sources: Chenzhou First People's Hospital 2022 High-Quality Development Annual Project (2022KJ-233); Bethune Charitable Foundation Enze Pain Management Medical Research Project (ezmr2022-016); Medical Research Fund of Hunan Medical Association (2021109101425); Research Project of Xiangnan University (2021XJ163).

Declaration

All authors listed declare that they have no conflicts of interest.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2023.52.008185

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