Ketorolac tromethamine pretreatment suppresses sufentanil-induced cough during general anesthesia induction: a prospective randomized controlled trial

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Abstract

Background: To observe the effect about pretreatment of ketorolac tromethamine on sufentanil-induced cough in general anesthesia patients.

Methods: 102 patients were screened, and a total of 90 patients were scheduled for elective surgery under general anesthesia. 90 patients were randomly divided into two groups: the control group（C group）and the observation group（KT group）. 5 minutes before anesthesia induction, observation group were given ketorolac tromethamine 0.5mg/kg intravenously within 3 s, while the control group were given the same amount of normal saline intravenously. All patients were given a sufentanil bolus of 0.5 ug/kg（within 3 s） intravenously,1 minute later, propofol 2.5mg/kg, vecuronium 0.15mg/kg were injected intravenously, and endotracheal intubation was guided by laryngoscope. The number of coughs that occurred within 1 min after sufentanil injection were recorded. The mean arterial pressure (MAP)、heart rate (HR) and pulse oxygen saturation(SpO2) were recorded at T0 (immediately before pretreatment), T1 (5 minutes after pretreatment), T2（before intubation）、T3 (1 min after intubation) and T4 (5 min after intubation).The incidence of adverse reactions were analyzed.

Results: Within 1 min after sufentanil injection, the incidence and severity of cough in KT group was significantly lower than that in C group ($P < 0.05$). At the time points of T0, T1, T2, T3 and T4, there was no significant difference in MAP, HR and SpO2 between the two groups ($P > 0.05$). And there was no significant difference in the dosage of sufentanil, propofol, remifentanil and vecuronium, incidence of nausea and vomiting, delay of recovery, dizziness, drowsiness and respiratory depression between the two groups($P > 0.05$). However, there were significant differences in the number of restlessness during waking period ($P < 0.05$).

Conclusion: Pretreatment of intravenous ketorolac tromethamine can significantly reduce the incidence of sufentanil-induced cough during induction period of general anesthesia patients, and can also significantly reduce the restlessness during recovery period of patients. Trial registration: Chinese Clinical Trial Registry (registration number# ChiCTR2000030287; date of registration: 27/02/2020).

Background

Sufentanil, commonly used in general anesthesia with strong analgesic properties,can produce an irritating cough during the intravenous induction [1, 2]. Studies showed that 25–42% patients experienced this kind of cough reaction after intravenous injection of sufentanil [2, 3]. Sometimes, the cough reaction will be explosive or spasmodic, which will cause a sharp rise in blood pressure, intracranial pressure, intraocular pressure, intrapulmonary pressure and abdominal pressure. Therefore，for patients with hypertension, intracranial hypertension, pulmonary bullae, hemangioma and high intra-abdominal pressure, the risks of anesthesia induction period will be significantly increased when using sufentanil [4].

Various agents have been used to suppress cough during induction of general anesthesia [5, 6], such as remifentanil, dexmedetomidine, magnesium sulfate, lidocaine, and dezocine, etc. However, the clinical

application was somewhat limited due to their more or less potential additional side effects including sharp decrease of heart rate and blood pressure, myocardial inhibition, respiratory depression, long onset time, long duration and low effective rate[7, 8]. Therefore, it is a challenge for anesthesiologists to find a more safe and effective drug with less adverse reactions to inhibit sufentanil-induced cough response during induction of general anesthesia.

Aspirin is a common nonsteroidal anti-inflammatory and analgesic drug. Alexander T et al.[9] reported that moderate dose aspirin (500 mg/day) could reduce angiotensin converting enzyme inhibitor-induced cough. Ketorolac tromethamine is a new nonsteroidal anti-inflammatory and analgesic drug, which is widely used in the short-term treatment of acute moderate and severe pain including various postoperative incision pain[10, 11]. At present, the clinical effect and safety of ketorolac tromethamine on suppressing sufentanil-induced cough during induction of general anesthesia remain unclear.

The purpose of this study is to investigate the effectiveness of ketorolac tromethamine on treating sufentanil-induced cough response by intravenous injection prior to general anesthesia induction.

Methods

The prospective randomized controlled trial was performed in accordance to CONSORT guidelines. This study was approved by the Institutional Research Ethics Committee of the Suqian people's Hospital of Nanjing Drum-Tower Hospital Group, Suqian, Jiangsu, China. The trial was registered on Chinese Clinical Trial Registry (No. Chi CTR2000030287). The written informed consent was obtained from each patient following principles of the Helsinki Declaration.

Participants

102 adult patients, ASA physical status I or II, aged 18–65 years, weighed 45 to 89 kg, BMI 18.0–30.0 kg/m^2, were enrolled in this study. The patients were scheduled for elective surgery under general anesthesia in Suqian people's Hospital of Nanjing Drum-Tower Hospital Group from Feb 2020 to Mar 2020. Exclusion criteria were that people has history of asthma, chronic cough, and upper respiratory tract infection within two weeks. Patients with history of peptic ulcer or bleeding, heart disease, aneurysm, liver disease, kidney disease, participated in other clinical trials or researchers considered inappropriate to participate in this experiment were also excluded. Ninety patients were randomly divided into two groups via computer-generated random numbers list: control group (C Group, n = 45) and ketorolac tromethamine group (KT Group, n = 45).

No patient received premedication in this study. In the operating room, noninvasive blood pressure (NBP), pulse oxygen saturation (SpO_2), electrocardiogram (ECG) were routinely monitored. Patients were cannulated through forearm median cubital vein with a 20G venous trocar needle. Five mins before general anesthesia induction, KT group patients were given ketorolac tromethamine 0.5 mg/kg (diluted to 5 ml using normal saline) intravenously within 3 s, while those in C group were given normal saline 5 ml

only. Ketorolac tromethamine or normal saline was prepared by a nurse anesthetist and implemented by an experienced anesthesiologist who was blind to the procedure. All patients were given 100% oxygen via a face mask with an oxygen flow rate of 5L/min for 3 min. General anesthesia was induced with a bolus of sufentanil 0.5 μg/kg within 3 s intravenously, and 1 minute later, propofol 2.5 mg/kg and vecuronium 0.15 mg/kg were infused sequentially. Endotracheal intubation was performed using the Macintosh laryngoscope. The depth of general anesthesia was maintained under propofol 5 mg/kg/h, remifentanil 10 μg/kg/h and vecuronium 0.05 mg/kg/h and was adjusted based on vital signs of the patients.

The frequency of cough within 1 min following sufentanil injection was recorded and the severity was graded depending on the cough frequency (mild, 1–2; moderate, 3–4; severe,≥5)[12, 13].

The mean arterial pressure (MAP), heart rate (HR) and S_PO_2 were recorded at the following time-points: T0, before pretreatment of ketorolac tromethamine or normal saline /baseline value; T1, 5 min after pretreatment; T2, before intubation; T3, 1 min after intubation, and T4, 5 min after intubation. The incidence of adverse reactions including nausea and vomiting, dizziness, drowsiness, delay of recovery, restlessness in recovery period and respiratory depression were analyzed.

Sample size determination

In our preliminary study, the incidence of cough elicited by 0.5 μg/kg sufentanil infused within 3 s was 31.8% (7/22), which was reduced to 4.5% (1/22) when ketorolac tromethamine pretreatment was performed. To achieve 80% statistical power with α = 0.05, each group would require no less than 33 cases. Considering there may be a drop rate of 20%, we recruited 51 patients for each group to allow missing data.

Statistical analysis

SPSS 22.0 software (IBM Corp, Armonk, NY, USA) was used for statistical analysis. The presented data were evaluated for normal distribution by Kolmogorov–Smirnov test. Measurement data were presented as the mean ± standard deviation and Student's t-test was used to assess the difference between two groups. The difference of ranked data were analyzed by Mann–Whitney U test. Chi-square test or Fisher's exact test was adopted to assess the difference of categorical data presented as absolute or relative effect sizes. *P*-value < 0.05 was considered significant.

Results

Among 102 patients, 5 patients refused to participate in the study, 4 patients had a history of hypertension, and 3 patients underwent the change of anesthesia protocol (Fig.1), so 90 patients were enrolled in further study. There were no significant differences in gender, age, weight, BMI, ASA physical status and anesthesia time between the two groups (P > 0.05) (Tab 1).

The incidence and severity of cough within 1 min after sufentanil injection in KT group was significantly lower than that in C group (*P* < 0.05) (Table 2).

There were no significant differences in MAP, HR and SpO2 between the two groups at the different time points of T0, T1, T2, T3 and T4 ($P > 0.05$) (Table 3).

There was no significant difference in the dosage of sufentanil, propofol, remifentanil and vecuronium between the two groups ($P > 0.05$) (Table 4).

The incidences of agitation in anesthesia recovery period in KT group were lower significant than those in C group ($P < 0.05$). There were no significant differences in the incidences of nausea and vomiting, delay of recovery, dizziness, drowsiness or respiratory depression between the two groups ($P > 0.05$) (Table 5).

Fig 1. Flow chart of patients participating in this study

Table 1 Demographic data and basic clinical characteristics of the patients in two groups

	C Group	KT Group	*P* value
Gender (male/female)	19/26	21/24	> 0.05
Age (year)	47.8±8.9	48.1±9.1	> 0.05
ASA (I/II)	28/17	30/15	> 0.05
Weight (kg)	69.8±10.2	69.4±9.9	> 0.05
BMI (kg/m^2)	24.6±3.4	24.9±3.1	> 0.05
Anesthesia time (min)	95.9±20.8	97.0±21.0	> 0.05

Values are expressed as mean ± standard deviation

Table 2 Incidence and severity of cough in two groups

Groups	Incidence of cough	Severity of cough n (%)			
	n (%)	None	Mild	Moderate	Severe
C group	14(31.1)	31(68.9)	3(6.7)	11(24.4)	0(0.0)
KT group	3(6.7)	42(93.3)	2(4.4)	1(2.2)	0(0.0)
P value	< 0.05	< 0.05			

Table 3 Comparison of MAP, HR and SpO2 values at different time points

Groups		T0	T1	T2	T3	T4
C group	MAP(mmHg)	94.7±11.2	94.0±9.8	84.3±10.5	90.9±10.9	82.7±9.5
	HR(bpm)	76.3±7.5	75.8±6.2	69.2±7.4	79.1±7.1	68.7±6.4
	SpO_2（%）	98.1±1.2	97.8±0.9	99.0±0.7	99.0±0.8	99.0±1.0
KT group	MAP(mmHg)	93.9±11.5	93.4±9.6	83.9±10.2	89.2±10.3	81.9±9.3
	HR(bpm)	75.9±7.3	75.2±6.0	68.9±7.6	78.8±7.0	68.4±6.6
	SpO_2（%）	97.9±1.0	97.7±0.8	98.8±0.7	99.0±1.0	99.2±0.5

Values are expressed as mean ± standard deviation

Table 4 Comparison of anesthetic dosage between two groups

Groups	C group	KT group	*P* value
Sufentanil (ug)	39.2±8.0	38.7±7.8	> 0.05
Propofol(mg)	640.4±85.4	629.3±84.5	>0.05
Vecuronium(mg)	17.0±3.8	16.5±3.6	> 0.05
Remifentanil(mg)	1.2±0.3	1.1±0.2	> 0.05

Values are expressed as mean ± standard deviation

Table 5 Comparison of adverse reactions during anesthesia recovery n (%)

Groups	C group	KT group	*P* value
Nausea and vomiting	3(6.7)	4(8.9)	> 0.05
delay of recovery	1(2.2)	2(4.4)	> 0.05
dizziness	3(6.7)	3(6.7)	> 0.05
drowsiness	2(4.4)	3(6.7)	> 0.05
restlessness in waking period	7(15.6)	1(2.2)	< 0.05
depressed respiration	0(0.0)	1(2.2)	> 0.05

Discussion

At present, sufentanil, fentanyl and other opioid analgesics injected intravenously during the induction period of clinical anesthesia showed strong analgesic effect and little influence on hemodynamic indexes [14, 15], and can effectively inhibit tracheal intubation response (such as increased heart rate, increased blood pressure, etc.)[16, 17]. However, it is easy to cause choking and coughing reaction in different degrees within 1 min of intravenous injection[18]. For patients with hypertension, pulmonary bullae, hemangioma and intracranial hypertension, it may cause severe consequences.

The various incidence among different studies might be due to the different doses of sufentanil used and the differences in concentrations, administration rate, race and age[19]. In an study by Agarwal et al. [20] sufentanil 0.3 μg/kg injected over 5 s elicited cough in 15.8% of patients, while in another study by Li et al. [21] the incidence of cough was 37% after the injection of sufentanil 0.5 μg/kg within 3 s, with a high dose of sufentanil (1 μg/kg), the incidence of sufentanil-induced cough could be up to 45.8%. We have previously considered that large doses of sufentanil can lead to prolonged recovery time, while small doses of sufentanil can not meet the needs of surgery analgesia. In our study, we administered sufentanil 0.5 μg/kg intravenously within 3 seconds before operation in the C group of normal saline. Within 1 minute, the incidence of sufentanil induced cough was 31.1%.This is similar to the conclusion of relevant research.

A lot of studies have been done on the mechanism of sufentanil induced cough response, but the relevant mechanism is still not very clear[3–5]. It may be related to sufentanil activating the C-fiber receptor of the bronchus, adapting the pulmonary stretch receptor (RARs), inducing the airway hyperresponsiveness, inhibiting the efferent impulse of the sympathetic nerve, making the vagus nerve in a comparative advantage, and finally leading to the occurrence of the choking cough response[5, 6].

To provide patients with safe and comfortable medical experience is also the responsibility of anesthesiologists. Flurbiprofen axetil is a nonsteroidal drug commonly used in clinic. Geng W J, et al.[22] reported that using 100 mg flurbiprofen axetil before operation can significantly reduce the incision pain,

reduce the excitement and systemic inflammation of patients after operation. Fukumori N, et al [23] investigated 71 patients with total hip replacement in Japan and found that intravenous acetaminophen can significantly reduce the pain of patients within 24 hours after early operation. The pretreatment of ketorolac tromethamine injection also played a role in the recovery period of anesthesia, significantly reducing the postoperative incision pain of patients, and the incidence of restlessness caused by pain and other adverse stimulation naturally decreased significantly. To a certain extent, it provided patients with comfortable medical experience and humanistic care.

Ketorolac tromethamine is a new nonsteroidal anti-inflammatory drug (NSAID). Motov S, et al. [24] found that intravenous infusion of ketorolac tromethamine of 30 mg can significantly improve the moderate to severe pain of emergency patients. Studies by Yang H L et al.[25]suggested that the use of injection of ketorolac tromethamine before tracheal intubation can reduce the percentage of sore throat caused by endotracheal intubation from 71.6–21.1%. Compared with other NSAID, ketorolac tromethamine has less anti-inflammatory effect and stronger analgesic effect, which has been widely used in clinic [10, 26]. At present, there are few reports about ketorolac tromethamine reducing sufentanil-induced cough response. It has been reported that intravenous injection of dezocine before anesthesia induction can inhibit the cough response induced by sufentanil or fentanyl to some extent by activating *K* receptor and inhibiting histamine release[5].Considering that ketorolac tromethamine is a nonsteroidal anti-inflammatory drug, the mechanism of ketorolac tromethamine injection reducing cough response may be related to the reduction of histamine release and other reasons [10, 26].

In order to evaluate the possible adverse reactions and safety of ketorolac tromethamine injection pretreatment, we compared the mean arterial pressure, heart rate and blood oxygen saturation values of the two groups of patients at different time points. The results of this study suggest that pretreatment of ketorolac tromethamine injection would not have adverse effects on vital signs of patients.

5 minutes before anesthesia induction, intravenous ketorolac tromethamine 0.5 mg/kg pretreatment can significantly reduce the incidence of choking and coughing reaction in induction period of general anesthesia patients, and can significantly reduce restlessness in recovery period of patients, which is safe and economic.

There are also some deficiencies in our research. First, due to the limitation of objective conditions, we have not studied the mechanism of ketorolac tromethamine inhibiting cough response and can not give more reasonable inferences about the relevant mechanisms. We just describe the relevant effects objectively, because there is no relevant report about ketorolac tromethamine injection or other nonsteroidal drugs inhibiting sufentanil-induced cough. Second, the pretreatment dose of ketorolac tromethamine (0.5 mg/kg) is not necessarily the most appropriate dose for ketorolac tromethamine to inhibit sufentanil induced cough response, but given according to the early postoperative analgesic dose of the drug instructions [10].Third, our study is a single center study with a small sample size. In order to determine whether pretreatment of ketorolac tromethamine injection can reduce sufentanil induced cough response, we still need a large sample and multicenter study.

Conclusions

Pretreatment of intravenous ketorolac tromethamine 0.5 mg/kg can significantly reduce the incidence of sufentanil-induced cough in induction period of general anesthesia patients, and can significantly reduce the restlessness of patients in recovery period, safe and economic. To a certain extent, it provided patients with comfortable medical experience and humanistic care, which is worth popularizing.

Abbreviations

NBP
noninvasive blood pressure;
SpO_2
pulse oxygen saturation;
ECG
electrocardiogram;
MAP
mean arterial pressure
HR
heart rate

Declarations

Ethics approval and consent to participate

This clinical trial was approved by the Institutional Research Ethics Committee of the Affiliated of Suqian people's Hospital of Nanjing Drum-Tower Hospital Group, Suqian, Jiangsu, China. All the participants provided written informed consent following principles of the Helsinki Declaration.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ZT designed the study, performed the statistical analysis, and drafted the manuscript. *BC* interpreted the data and revised the manuscript, collected the data and assisted in drafting the manuscript. *LW* revised the manuscript and approved the version to be published. *All authors* read and approved the final submitted version of the manuscript.

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Figures

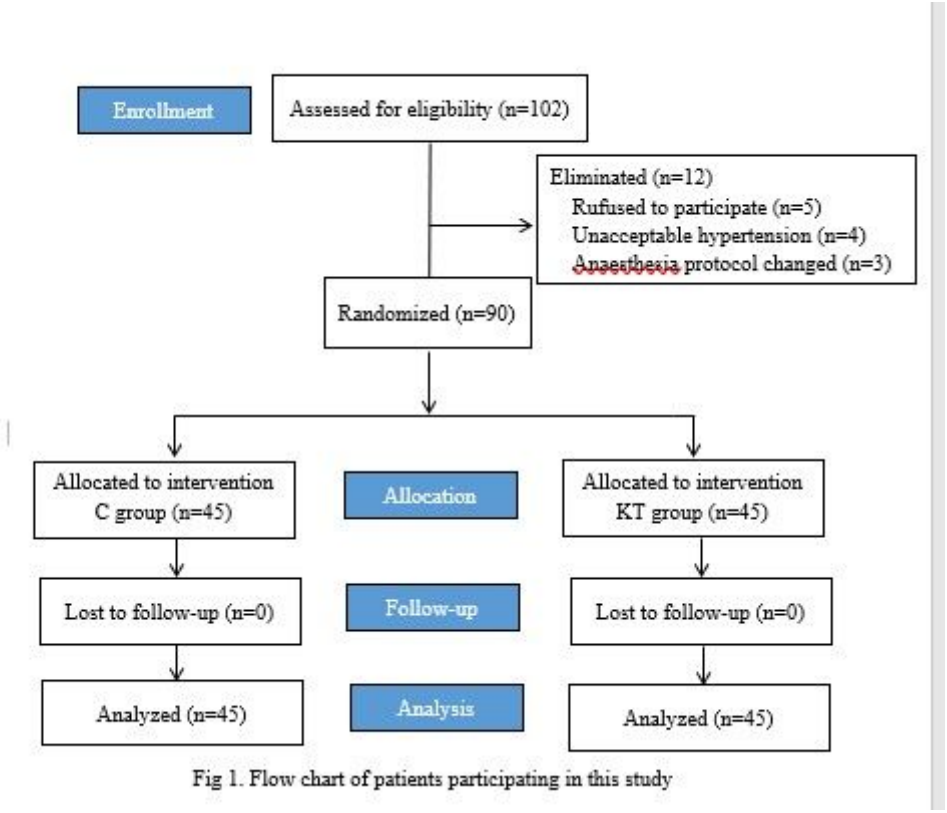

Figure 1

Flow chart of patients participating in this study

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- CONSORT2010Checklist.doc