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ORIGINAL RESEARCH

Transcutaneous electrical acupoint stimulation before induction of anesthesia reduces sufentanil-induced cough: a randomized, controlled trial

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Abstract

Background: Sufentanil-induced cough is a common side effect during the induction of general anesthesia. This study sought to determine the inhibitory effect of TEAS (transcutaneous electrical acupoint stimulation) on the incidence of sufentanil-induced cough.

Methods: A total of 339 patients were recruited of which 300 patients were enrolled and randomly allocated into five groups (n = 60): Patients did not receive TEAS in the control group (C group); patients received 2 Hz TEAS at LI4/PC6 (Hegu/Neiguan) in the 2A group; patients received 100 Hz TEAS at LI4/PC6 in the 100A group; patients received 2 Hz TEAS at ST36/SP6 (Zusanli/sanyinjiao) in the 2B group; and patients received 100 Hz TEAS at ST36/SP6 in the 100B group. With the exception of the C group, all groups received TEAS for 30 minutes before induction. 0.5 μg/kg of IV sufentanil was given over 2 seconds, and the occurrence of cough was observed and recorded for 1 minute. The severity of cough was graded as mild (1-2 coughs), moderate (3-5 coughs), and severe ($>$ 5 coughs). The mean arterial pressure (MAP) and heart rate (HR) before (T0) and 1 minute after (T1) sufentanil injection were recorded.

Results: The incidence of sufentanil-induced cough in C group, 2A group, 2B group, 100A group and 100B group were 37%, 27%, 27%, 12% and 13%, respectively. Compared with the C group, the incidence of cough in the 100A group and the 100B group were significantly lower ($P < 0.05$). The MAP and HR between the five groups were not statistically different.

Conclusion: The administration of 100 Hz TEAS for 30 minutes before sufentanil injection can effectively reduce the incidence of sufentanil-induced cough during the induction of general anesthesia.

Keywords

Sufentanil; Cough; TEAS; General anesthesia

1. Introduction

Sufentanil, an opioid anesthetic, is widely used in clinical anesthesia due to its strong analgesic effect, rapid-onset, and stable cardiovascular effects. However, intravenous (IV) sufentanil injection can evoke a cough reflex, which may increase the risk of anesthesia. A previous report [1] showed that the incidence of sufentanil-induced cough is 28% in Asian patients. Although sufentanil-induced cough is usually transient and benign, it may result in serious complications in patients with ocular trauma, pneumothorax, a reactive/difficult airway, aortic dissection, or patients undergoing neurosurgery [2]. During the COVID-19 pandemic, coughing during induction increases the risk of transmission of the virus to the anesthesiologist [3].

Previous studies have reported various approaches to suppress sufentanil-induced cough during anesthetic induction. These approaches have included pre-induction with IV lidocaine, ephedrine [4], dexamethasone [5], ketamine [6], clonidine [7], dexmedetomidine [1], and β-receptor blocker inhalation [8]. However, due to the side effects of these drugs, these methods are not widely used.

Transcutaneous Electrical Acupoint Stimulation (TEAS) has an analgesic effect, reduces the perioperative inflammatory response, and promotes immune function and oxygenation [9]. TEAS has been proven to have a significant effect on the treatment of lung diseases, such as COPD and asthma [10, 11], however TEAS has not been used to prevent sufentanil-induced cough. We therefore sought to determine whether patients receiving TEAS before anesthetic induction can effectively reduce sufentanil-induced cough, in a randomized, controlled clinical trial.

2. Materials and methods

This study was conducted after approval from the ethics committee of the First Affiliated Hospital of Wenzhou Medical University (2016-142) (Wenzhou, China) and registered at the Chinese Clinical Trial Registry (ChiCTR-INR-16008759). Written informed consent was obtained from all patients.

The inclusion criteria included age 20 through 75 years, with an ASA physical status of I or II, undergoing elective surgical procedures under general anesthesia.

The exclusion criteria were as follows: any incision or surgical scar in an acupoint; infection in an acupoint; nerve injury in the upper or lower limbs; a history of spinal surgery; allergic reaction to drugs used in the study; sinus bradycardia; severe neurological disease (intracranial hypertension, cerebral hernia, cerebral tumor, cerebral aneurysm); severe respiratory disease (asthma, pneumothorax, chronic obstructive pulmonary disease, bronchial hyperresponsiveness); smoking; severe cardiovascular disease (myocardial infarction, aortic dissection); addiction to anaesthetic or recent history of opioid use; upper respiratory tract infection in the previous 2 weeks; biliary tract surgery; or treatment with angiotensin-converting-enzyme inhibitors (ACE-inhibitors).

This study was conducted from August 2016 to July 2019 at the First Affiliated Hospital of Wenzhou Medical University. 300 patients were randomly divided into five groups (n = 60): Patients did not receive TEAS in the control group (C group); patients received 2 Hz TEAS at the bilateral LI4/PC6 in the 2A group; patients received 100 Hz TEAS at the bilateral LI4/PC6 in the 100A group; patients received 2 Hz TEAS at the bilateral ST36/SP6 in the 2B group; patients received 100 Hz TEAS at the bilateral ST36/SP6 in the 100B group. The locations of all the acupoints are shown in Fig. 1.

Except for the C group, other groups received TEAS for 30 minutes before induction of anesthesia. Venous access was established using a 22 G cannula on the dorsum of the non-dominant hand before entering the operating room. No medication other than crystalloids were given. Upon arrival in the operating room, non-invasive blood pressure recordings, oxygen saturation values, and electrocardiography were recorded. The anesthesia induction sequence was started with intravenous sufentanil (0.5 μg/kg) over two seconds. An independent observer recorded the occurrence of cough after sufentanil administration after 1 minute. The severity of cough was graded as mild (1-2 coughs), moderate (3-5 coughs), and severe ($>$ 5 coughs). After this observation period, propofol (2 mg/kg) and rocuronium (1 mg/kg) were given and endotracheal intubation was performed. Mean Arterial Pressure (MAP) and Heart Rate (HR) before (T0) and 1 minute after (T1) sufentanil injection were recorded.

During the time from sufentanil administration to successful endotracheal intubation, an oxygen mask was applied if the blood oxygen saturation was $<$ 90%; norepinephrine was given if the systolic blood pressure (SBP) was $<$ 90 mmHg or the diastolic blood pressure (DBP) was $<$ 60 mmHg; and atropine 0.5 mg was given if the HR was $<$ 50/min.

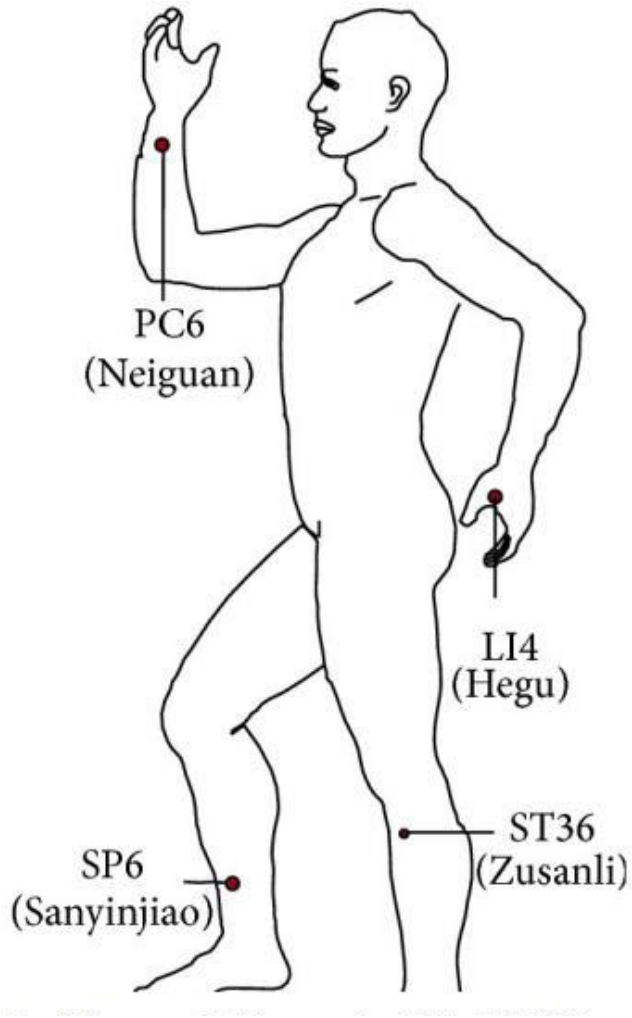

FIGURE 1. 2A group and 100A group received TEAS at PC6/LI4; 2B group and 100B group received TEAS at SP6 and ST36.

2.1 Statistical analysis

The required sample size was estimated based on a 30% reported incidence of sufentanil-induced cough, and an assumption that TEAS would reduce the incidence of cough to 8%, according to a pilot study. With α = 0.05 and β = 0.20, a minimum of 60 patients per group were required.

We used a randomization table to randomize patients. The random numbers were divided by 5; the remainder of the division sum (0, 1, 2, 3, 4) was used to decide the allocation to each of the 5 groups.

SPSS 20.0 software was used for statistical analyses. Data were expressed as mean $\pm$ standard deviation, and ANOVA was used to assess the differences between the five groups. The categorical data were compared using the chi-square test. $P <$ 0.05 was considered statistically significant.

3. Result

A total of 339 patients were recruited from August 2016 to July 2019, 39 patients were removed because they did not meet the inclusion criteria, and 300 patients were enrolled (5 patients with a history of asthma, 19 patients were smokers, and 15

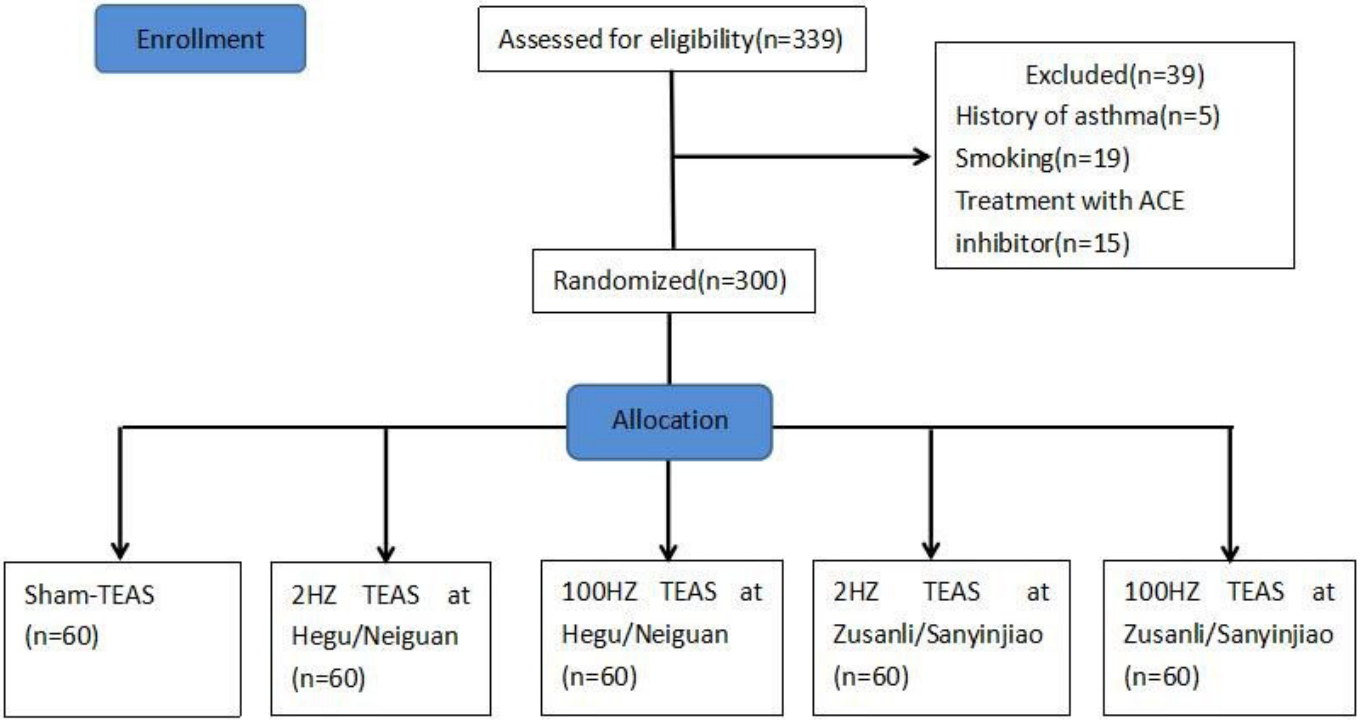

FIGURE 2. Number of patients included and exclued.

TABLE 1. Characteristics of the patients.

	C group	2A group	2B group	100A group	100B group	*P* value
Age, years	47 (13)	47 (14)	48 (13)	47 (12)	48 (12)	0.603
Sex, M/F	17/43	13/47	16/44	19/41	15/45	0.790
Weight, kg	62 (11)	61 (11)	62 (11)	61 (12)	61 (10)	0.589
Height, cm	161 (7)	162 (7)	163 (7)	161 (8)	161 (7)	0.273
ASA 1/2	23/37	26/34	21/39	20/40	19/41	0.696

Values are the mean (SD). The Characteristics of patients did not differ significantly in the 5 groups ($P > 0.05$).

patients were taking an ACE inhibitor) (Fig. 2).

The patient characteristics (age, weight, sex) in the 5 groups were not statistically different (Table 1). The incidence of sufentani-induced cough in the C group, 2A group, 2B group, 100A group and 100B group were 37%, 27%, 27%, 12% and 13%, respectively. Compared with the C group, the incidence of cough in the 100A group and 100B group were significantly lower ($P < 0.05$) (Table 2). However, the severity of cough was not statistically different amongst the groups using ANOVA testing (Table 2). The MAP and HR between the five groups were not statistically different (Table 3). After the injection of sufentanil, none of the patients developed decreased blood oxygen saturation ($SpO_2 < 90\%$), hypotension, apnea, nausea, vomiting, or any other adverse reactions.

TABLE 2. Incidence of cough.

Groups	Incidence of cough (n%)	Severity of cough		
		Mild	Moderate	Severe
C group	22 (37)	12	7	3
2A group	16 (27)	8	7	1
2B group	16 (27)	7	7	2
100A group	7 (12)*	4	2	1
100B group	8 (13)*	4	2	2
P value	0.005	0.949		

Values are the number (proportion).$P < 0.05$ compared with C Group, The P values of group 100A and group 100B were 0.003 and 0.001, respectively. The severity of coughing was not significantly difference among the groups ($P > 0.05$).*

4. Discussion

Our study revealed that using TEAS at a frequency of 100 Hz for 30 min at the bilateral LI4/PC6 and ST36/SP6 acupoints before induction of general anesthesia can significantly reduce the incidence of sufentanil-induced cough.

Sufentanil is a synthetic opioid drug that is widely used for the rapid induction of anesthesia. However, IV injection of sufentanil can evoke coughing, which increases the risks associated with anesthesia. Li *et al.* [12] found that the use of

TABLE 3. The mean arterial pressure (MAP) and the heart rate (HR) before (T0) and after (T1) sufentanil administration.

	HR (bpm)		MAP (mmHg)	
	T0	T1	T0	T1
C Group	80 (12)	79 (11)	97 (14)	96 (13)
2A Group	79 (14)	79 (14)	100 (16)	99 (16)
2B Group	77 (11)	76 (11)	94 (11)	94 (12)
100A Group	77 (13)	77 (13)	101 (13)	98 (13)
100B Group	81 (12)	81 (11)	95 (12)	96 (12)
P value	0.135		0.08	

Values are the mean (SD). The HR and MAP before and after sufentanil administration did not differ significantly in the 5 groups ($P > 0.05$).

peripheral IV sufentanil 0.5 μg/kg during anesthetic induction was associated with a 37% incidence of cough. An *et al*. [13] found that the incidence of sufentanil-induced cough could be decreased by 45.8% using 1 μg/kg sufentanil.

Several mechanisms may explain sufentanil-induced cough [14, 15]. ① Opioid receptors are divided into μ, κ, δ, σ types, depending on their activation. It is possible that a particular type of opioid receptor present in the airway plays an important role in mediating the sufentanil-induced cough. ② Acute conditioning of rapidly adapting stretch receptors (RARS) and C-fibers may play a role. In particular, the laryngeal and tracheal RARS in the bronchial tree, probably act as the primary sensory pathways of the cough reflex. C-fibers can not only induce cough by releasing tachykinin, which activates RARS, but can also cause neurogenic inflammation, and inhibit the cough reflex through a central gating mechanism. Intravenous sufentanil may cause bronchial smooth muscle contraction, and activation of RARS in the adjacent regions which may cause coughing. ③ Airway high reactivity (AHR) is also considered to play a role in sufentanil-induced coughing.

Previous studies have sought to suppress sufentanil-induced cough by injecting exogenous drugs, such as lidocaine, ephedrine [4], dexamethasone [5], ketamine [6], clonidine [7], and dexmedetomidine [1]. However, these drugs may result in side effects such as hemodynamic instability and arrhythmias.

Electroacupuncture is widely used as an analgesic [16] and as a means to preserve perioperative organ function [17, 18]. Previous studies have suggested that the endogenous opioid peptides enkephalin, beta-endorphin, and dynorphin are involved in mediating the analgesic effect of electroacupuncture [19]. Another study demonstrated that low and high frequency TEAS, given for 30 min, could increase the enkephalin and dynorphin levels in lumbar cerebrospinal fluid (CSF) [20].

In our study, we found that patients who received 100 Hz can effectively prevent sufentanil-induced cough, either LI4/PC6 or ST36/SP6. We hypothesized that the mechanism for this phenomenon is the increase of dynorphin in CSF after TEAS. The production of endogenous opioid peptides is the basis of electroacupuncture analgesia. Abundant opioid receptors are located in the central nervous system (CNS), such as the head of the caudate nucleus, the nucleus accumbens, the amygdaloid nucleus, the periaqueductal gray, and the nucleus raphe magnus [21]. With changes in electroacupuncture frequency, opioid peptides production will also change. Low frequency electroacupuncture produces enkephalin, while high frequency electroacupuncture produces dynorphin, either LI4/PC6 or ST36/SP6 [20, 22, 23]. Opioids may inhibit cough reflex by acting directly on the cough center in the medulla. A highly selective κ-opioid receptor agonist has potent antitussive effects when administered either IV. or intraperitoneal (IP). μ2- rather than μ1-opioid receptors are involved in the μ-opioid receptor-induced antitussive affects [24, 25]. Therefore, we suggest that a possible mechanism underlying this phenomenon is the 100 Hz TEAS-mediated release of dynorphin into the CSF, leading in part to κ-receptor activation, which could then have an antitussive effect, while the endorphins produced by 2 Hz TEAS could not selectively activate the μ2-receptor.

In addition, a previous study [26] found that sedation could inhibit sufentanil-induced cough; therefore, the sedative effect of TEAS may be one of the reasons for inhibition of sufentanil-induced cough by TEAS.

In recent years, there has been an increase in the use of electroacupuncture in the perioperative period. This study has found a new role for electroacupuncture in the perioperative period, and suggests the need for further studies to determine the mechanism by which electroacupuncture decreases sufantinal-induced cough during general anesthesia.

This study had some limitations. First, we could not use an antagonist in patients. Second, we only chose the number of coughs as the primary outcome, and did not investigate any other biochemical factors in our study. Third, the size of the electrode slice we used was 3.5 cm $\times$ 3.5 cm, which was too large to avoid affecting other acupoints; therefore, we did not set up a non-acupoint group. These limitations should be addressed in future studies.

5. Conclusions

Patients receiving 100 Hz TEAS for 30 min before sufentanil injection can effectively reduce the incidence of sufentanil-induced cough during the induction of general anesthesia.

AUTHOR CONTRIBUTIONS

Junjie Xie and Junlu Wang designed the study. Junkai Wang, Lili Yang, and Haijuan He collected the data. Junjie Xie and Yunchang Mo analyzed the data. Junjie Xie analyzed the results and drafted the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted after approval from the ethics committee of the First Affiliated Hospital of Wenzhou Medical University (2016-142) (Wenzhou, China) and registered at the Chinese Clinical Trial Registry (ChiCTR-INR-16008759). Written informed consent was obtained from all patients.

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CONFLICT OF INTEREST

All authors declare that they have no conflict of interests.

CONSENT FOR PUBLICATION

All authors have given full consent for publication.

DATA AVAILABILITY

The data used to support the findings of this study are available from the corresponding author upon request.

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