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Effect of transcutaneous electrical acupoint stimulation on the EC_{50} of remifentanil suppressing responses to tracheal extubation in elderly patients

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Abstract

Transcutaneous electrical acupoint stimulation (TEAS) is a emerging treatment which combines transcutaneous electrical nerve stimulation with traditional acupoint therapy. The present study was aimed to evaluate the effect of TEAS on the effective concentration (EC_{50}) of remifentanil suppressing tracheal extubation response in elderly patients.

Fifty-three patients undergoing spine surgery were randomly divided into 2 groups: control group (group C, n = 26) and *transcutaneous electrical acupoint stimulation group* (group TEAS, n = 27). The EC_{50} values for remifentanil TCI were determined using sequential method and probit analysis.

The remifentanil EC_{50} of that suppressed responses to *extubation* during anesthetic emergence was 1.20 ng/mL in group TEAS, a value that was significantly lower than the 1.64 ng/mL needed by patients in group C.

The TEAS can enhance the efficacy of remifentanil on *suppressing* responses to tracheal extubation in elderly patients, the EC_{50} of remifentanil can reduce approximately 27% compared with group C.

Abbreviations: ASA = American Standards Association, BIS = bispectral index, BMI = body mass index, HR = heart rate, MAP = mean arterial pressure, TEAS = transcutaneous electrical acupoint stimulation.

Keywords: cough, elderly, extubation, remifentanil, transcutaneous electrical acupoint stimulation

1. Introduction

During the tracheal extubation after general anesthesia, the mechanical irritation of sputum suction and extubing can not only induce airway reflexes such as cough and bronchospasm, but also hemodynamic fluctuations such as hypertension, tachycardia, arrhythmia which consequently can lead to the cardio-cerebral vascular accidents and even endanger life in severe cases.[1,2] Furthermore, due to the age-related decrease in functional reserve, and the increased prevalence of frailty and comorbidities, the risks of cardiovascular and cerebrovascular matters during extubation may be higher in elderly patients. Therefore, it is important for anesthetists to prevent and control the response to tracheal extubation to ensure smooth emergence from anesthesia.

There have been various methods to reduce the incidence of response during tracheal extubation. These include extubation while the patients under deep anesthesia;[3] administration of local anesthetics;[4] and infusion of various drugs like dexmedetomidine, short-acting opioids and vasodilators.[5–7] Remifentanil, a potent ultrashort-acting opioid which is independently metabolized of renal and liver functions, has rapid onset and offset of drug effect.[8] Studies have shown that remifentanil can increase tracheal tube tolerance,[9] continuous intravenous infusion of remifentanil during general anesthesia extubation can reduce the cough response and hemodynamic disorder caused by extubation,[2,10] however, remifentanil may delay emergence from anesthesia.[11]

In recent years, acupuncture assisted anesthesia and transcutaneous acupoint electrical stimulation (TEAS) have been suggested as an alternative to drugs for pain treatment. The TEAS is a complementary and alternative treatment method combines transcutaneous electrical nerve stimulation therapy with traditional acupuncture point therapy.[12] Indeed, TEAS is a new model of acupuncture with analgesic effect which characterized by non-invasive, easy-to-operate, and highly accepted among patients. Stimulating different acupoints can produce diverse curative effects. As a rule of thumb, acupuncture points related to painful diseases such as Hegu, Neiguan, and Zusanli are generally selected. The TEAS can not only induce the release of a variety of central neurotransmitters and endogenous opioids but also reduce the

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C-PY and Y-NL contributed equally for this work. C-PY and Y-NL conceived and designed the study and wrote the paper, JZ and QZ collected data, Y-YG, FG and X-LW analyzed the data.

The authors have no conflicts of interest to disclose.

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stress response and the consumption of opioids.[13,14] Bai et al[15] reported that TEAS was effective in reducing the stress response, incidence of postoperative pain and complications and improving the quality during extubation in elderly patients.

However, to our knowledge, no definite study has yet confirmed the median effective concentration (EC_{50}) of remifentanil used under the condition of TEAS for smooth tracheal extubation during emergence from anesthesia. The purpose of this study is to evaluate the effect of TEAS on the EC_{50} of remifentanil suppressing responses to tracheal extubation in elderly patients.

2. Materials and methods

2.1. Ethics statement

The present study was approved by the Ethics Committee of the Third Hospital of Hebei Medical University and performed according to the principles of the Helsinki Declaration. The informed consent of this study was obtained from each participating patient.

2.2. Participants and inclusion criteria

This was a prospective study of 53 patients ages 65 to 80 years who underwent posterior lumbar interbody fusion under general anesthesia from December 2017 to June 2018 in the Third Hospital of Hebei Medical University, American Society of Anesthesiologists (ASA) Physical Status classes I or II. Patients had no apparent abnormality of cardiopulmonary, liver, and kidney function; no history of analgesic drug abuse and allergic in medicine; no severe hearing and visual impairment. There was no injury or infection in the skin around the acupoints. The characteristics of patients are shown in Table 1. They were randomly assigned into 2 groups: control group (group C) and transcutaneous electrical acupoint stimulation group (group TEAS).

2.3. Interventions

Upon arrival in the operating room, patients were monitored via electrocardiogram, heart rate (HR), pulse oxygen saturation (SpO_2), bispectral index (BIS) and invasive blood pressure. In group TEAS, the patients received TEAS treatment at bilateral Neiguan (PC6) and Hegu (LI4) which were identified in accordance with the TCM anatomic localization with Hwato SDZ-II electronic acupuncture instrument (Suzhou Medical Products Factory Co, Ltd) 30 minutes before anesthesia. The frequency appeared alternately at sparse-dense wave (2/100 Hz) and the intensity gradually increased from 1 mA until the maximum current that the patient could tolerate. The TEAS treatment continued until the operation was completed. In group C, only the electrode pads were attached on the corresponding acupoints, and no electrical stimulation was performed.

Anesthesia in both groups was induced by intravenous injection of midazolam 0.05 to 0.2 mg/kg, sufentanil 0.1 to 2 μg/kg, propofol 1.5 to 2.5 mg/kg, cisatracurium 0.15 mg/kg. Intubation was performed with a reinforced endotracheal tube (internal diameter 7.5 mm for males and 7.0 mm for females) 2 minutes later. Ventilation frequency was set to 12 times per minute, inspiratory expiratory ratio to 1.0:2.0 and mechanical ventilation was adjusted to maintain an end-tidal CO_2 between 35 and 45 mm Hg using 100% concentration of oxygen with the flow to 2 L per minute. Anesthesia was maintained with continuous infusion of propofol 4 to 8 $mg\,kg^{-1}\cdot h^{-1}$ and remifentanil was injected with target effect-site concentrations of 1.5 to 5 ng/mL, which sustained the changing of BP and HR within 20% of the base levels and the BIS value range from 40 to 60. Before wound suturing, remifentanil was adjusted to a preconcerted level (e.g., 1.8 ng/mL for the 1st patient) and sustained for 15 minutes until tracheal extubation to ensure stable effect plasma concentration and effect-site concentration. Propofol infusion was stopped at the end of the operation, and 0.5 mg atropine plus 1.0 mg neostigmine were administered as muscle-relaxant antagonists. Tracheal extubation was performed when the SpO_2 was ≥ 95% and $P_{ET}CO_2$ was 35 to 45 mm Hg.

The target effect-site concentration (Ce) of remifentanil for each participant was determined by the response of the previous tested patient, via the up-and-down sequential method.[16] The 1st participant was measured at a 1.6 ng/mL Ce of remifentanil (step size of 0.2 ng/mL) in group TEAS and 2.0 ng/mL Ce of remifentanil in group C according to the previous studies and results of pretest experiment. The positive reaction to cardiovascular response: HR or mean arterial pressure (MAP) changes exceeded 20% of the base level. On the basis of literature,[17] the cough was graded: [0: no cough; 1: mild cough, only 1 time, no agitation; 2: moderate cough, > 1 time, but continued < 5 s, there is agitation but does not affect the extubation; 3: persistent cough> 5 s, with head-up, breath holding, cyanosis, etc]. Once MAP or HR exceed 20% of the basal value and/or moderate or severe cough appeared meant occurrence of extubation reaction, the target Ce of remifentanil for the next patient was increased by 0.2 ng/mL. Conversely, if extubation performed successfully the target Ce of remifentanil was decreased by 0.2 ng/mL. The anesthesiologist who performed tracheal extubation and assessed "success" or "failure" was unaware of the remifentanil Ce.

Table 1

Basic demographic data and anesthesia/surgery-related information.

	Group C (n = 26)	Group TEAS (n = 27)	*P* value
Age, y	72 ± 5	72 ± 3	.856
Weight, kg	71 ± 9	69 ± 9	.559
BMI	30.9 ± 5.5	29.5 ± 5.7	.386
Sex (male/female)	12/14	11/16	.691
ASA (I/II)	10/16	12/15	.659
Anesthesia time, min	140 ± 26	145 ± 29	.423
Operation time, min	116 ± 17	118 ± 15	.658
$P_{ET}CO_2$ (mm Hg)	43 ± 5	42 ± 6	.402

ASA = American Society of Anesthesiologists, BMI = body mass index.
Values are number or mean ± standard deviation (SD).

2.4. Data collection and index detection

The MAP, SpO_2, and HR were recorded baseline that is 0 minutes before TEAS (T_0), 15 minutes before extubation (T_1), at tracheal extubation (T_2), 1 minute after extubation (T_3), and 5 minutes after extubation (T_4), as same as $P_{ET}CO_2$ at tracheal extubation. The operation time and anesthesia time were recorded. Adverse effects including tracheospasm, aspiration and respiratory depression were recorded.

2.5. Statistical analysis

Statistical analysis was performed with the SPSS (version 21; SPSS, Inc., Chicago, IL). The modified sequential method and

Table 2

Comparison of the hemodynamic profile between the 2 groups at different time points (mean ± SD).

	MAP (mm Hg)		HR (beat/min)	
Time point	Group C (n=26)	Group TEAS (n=27)	Group C (n=26)	Group TEAS (n=27)
T_0	90.1±9.6	93.8±10.3	73.7±11.4	71.6±10.2
T_1	72.4±9.3*	71.1±10.0*	64.8±8.3*	63.2±11.6*
T_2	95.7±13.3	94.4±14.4	71.5±8.7	72.2±8.3
T_3	93.5±11.6	92.2±13.8	72.8±8.0	72.6±7.5
T_4	91.8±10.6	90.3±12.4	72.9±6.3	73.2±7.8

HR = heat rate, MAP = mean arterial pressure. T_0 (0 minutes before TEAS), T_1 (15 minutes before extubation), T_2 (at tracheal extubation), T_3 (1 minute after extubation), T_4 (5 minutes after extubation). Values are mean ± standard deviation (SD).

* $P < .05$ VS T_0.

All authors have read the journal policies and have no issues relating to journal policies. All authors have seen the manuscript and approved to submit to your journal. All authors declare that we have no conflict of interest regarding this study. The work described has not been submitted elsewhere for publication, in whole or in part.

Probit method were applied for the evaluation of EC_{50} of Remifentanil. All measurement data of normal distribution were expressed as the mean±SD. Comparisons between 2 groups were performed with independent-samples *t* test; Categorical data were presented as frequencies and percentages and were analyzed with the Chi-square test. Two-tailed probability value of $P < .05$ was considered as statistically significant.

3. Results

Transcutaneous electrical acupoint stimulation was successfully conducted on all the patients and none of them occurred any complications associated with anesthesia or surgery. Therefore, a total of 26 patients were analyzed for group C and 27 cases for group TEAS. Patients' characteristics and surgery/anesthesia-related variables including age, weight, body mass index (BMI), sex, ASA class, anesthesia time, and operation time were not different statistically between the 2 groups (Table 1).

The hemodynamic profiles of all patients were presented in Table 2. Before operation, there were no differences in MAP and HR between group C and group TEAS. Both in group C and group TEAS, the MAP at time T_1 decreased significantly when compared with its own preoperative value at time T_0 ($t = 6.744$, $P < .001$; $t = 8.198$, $P < .001$). HR had the parallel tendency at the same time in group C and TEAS ($t = 3.243$, $P = .002$; $t = 2.836$, $P = .006$). No patient had obvious bradycardia or hypotension.

As shown in Fig. 1, in group C, 1 patient achieved smooth tracheal extubation when the effect-site concentration (Ce) of remifentanil was 2.2 ng/mL; 3 of 4 patients achieved smooth tracheal extubation when the Ce of remifentanil was 2.0 ng/mL; 5 of 7 patients achieved smooth tracheal extubation when the Ce of remifentanil was 1.8 ng/mL; 4 of 8 patients achieved smooth tracheal extubation when the Ce of remifentanil was 1.6 ng/mL; 1 of 5 patients achieved smooth tracheal extubation when the Ce of remifentanil was1.4 ng/mL; 1 patient experienced failed smooth tracheal extubation when the Ce of remifentanil was 1.2 ng/mL. And, there were 15 of 27 patients achieved smooth tracheal extubation in group TEAS (Fig. 2). Dixon up-and-down method was applied to selecting 7 pairs of smooth/failed tracheal extubation data for the computation of the EC_{50} of remifentanil for smooth extubation during emergence from anesthesia in elderly patients. The probit analysis showed that the EC_{50} of remifentanil suppressing responses to tracheal extubation was 1.64 ng/mL (95% CI was 1.19–1.92 ng/mL) in group C and 1.20 ng/mL (95% CI was 0.77–1.43 ng/mL) in group TEAS, and there was significant difference between the 2 groups.

4. Discussion

The purpose of the present work was to determine the effect of TEAS on the EC_{50} of remifentanil suppressing responses to tracheal extubation in elderly patients by Dixon up-and-down

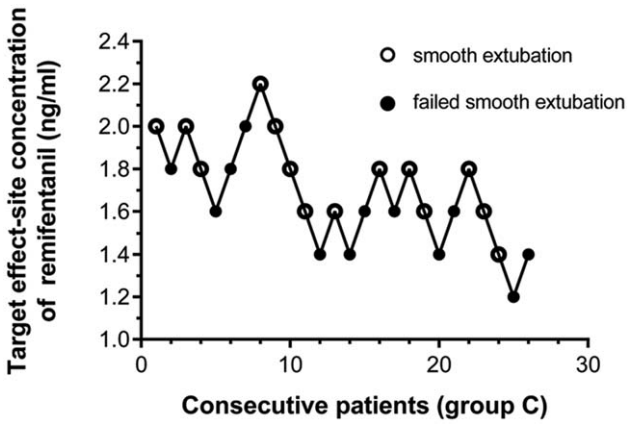

Figure 1. Sequences of effect-site concentration of remifentanil (with 2.0 ng/mL for the 1st person) for preventing responses to tracheal extubation during emergence in group C.

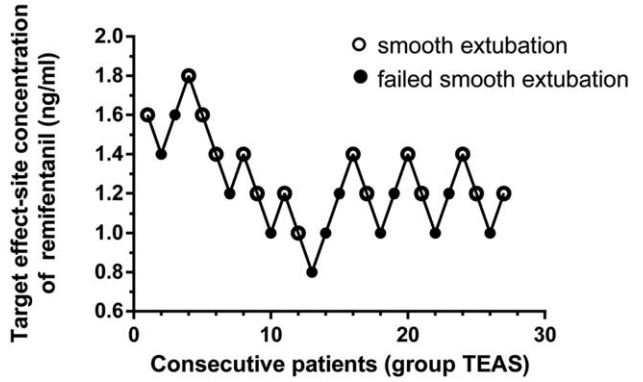

Figure 2. Sequences of effect-site concentration of remifentanil (with 1.6 ng/mL for the 1st person) combined with TEAS for preventing responses to tracheal extubation during emergence in group TEAS. TEAS = transcutaneous electrical acupoint stimulation.

method. The remifentanil EC_{50} of that suppressed responses to extubation during recovery of anesthesia was 1.20 ng/mL in group TEAS, a value that was significantly lower than the 1.64 ng/mL needed by patients in group C. There was about 27% decline between the 2 groups.

Although both TEAS and electroacupuncture have previously been applied to various researches, it should be registered that different studies used disparate parameters and acupoints to administer stimulation. On the basis of the theory of traditional Chinese medicine (TCM), the main reason of respiratory reactions during the extubation in patients with general anesthesia is the stimulation of the pulmonary system; consequently, acupoints that sustain energy flow balance in the pulmonary system and deliver analgesic effect were selected in our study to inhibit the stress response to extubation. Specifically, the Neiguan (PC6) acupoint belongs to the Hand-Jueyin Pericardium Meridian with the analgesic and sedative effect has been reported to alleviate PONV after surgery.[18,19] The Hegu (LI4) acupoint which belongs to the Hand-Yangming Large Intestine Meridian has been covered to be associated with analgesia and sedative effects.[20] A clinical trial found that stimulating the Hegu acupoint reduces the consumption of sevoflurane and narrows the time when spontaneous respiration recover, extubation, and eye open in patients performing supratentorial craniotomy.[21]

Studies have manifested that TEAS with low frequency stimulation motivates the release of β-endorphins, endomorphins, and enkephalin in both spinal cord and brain, causing excitation of the δ and/or μ opioid receptors and high frequency TEAS can induce dynorphin release in spinal cord.[14,22] Accordingly, we used sparse-dense wave (2/100 Hz) for treatment.

Several studies have indicated the usefulness of opioids for inhibiting the cough response during extubation. Combined with 1MAC sevoflurane, administration of remifentanil (0.03 μg/kg/min) was conducive to smooth tracheal extubation in adults.[3] Nevertheless, Shaja et al[23] has demonstrated that a remifentanil bolus dose (0.1 μg/kg) couldn't inhibit the cough response, only the cardiovascular responses during tracheal extubation. The antitussive effect of opioids is primarily central and the remifentanil's half-life is relatively short, therefore, a single dose of renifentanil was incapable of maintaining high enough plasma or effect-site concentrations. Then maintaining a certain effect site concentration of renifentanil with TCI is considered responsible. In several studies, a TCI of remifentanil during recovery from anesthesia could effectively decrease the tracheal extubation-related cough response and sustain hemodynamic stability.[24,25] Jun et al[26] have suggested that 1.5 ng/mL of remifentanil should be the ideal Ce to prevent cough response in the course of tracheal extubation, however, the dose of remifentanil could also induce delayed recovery from anesthesia.

Based on the former researches, the present study was performed aiming to determine the effect of TEAS on remifentanil suppressing responses to tracheal extubation in elderly patients and our results indicated that TEAS really decrease the EC_{50} of remifentanil which is consist with a prevenient study.[13] However, studies with different opinions that acupuncture treatment didn't reduce pain or analgesic consumption and the incidence of POVN have been published.[27–29] The reasons may go as follows: first, the acupuncture point stimulation may not have applied the expectant analgesic effect which used in other studies;[27] secondly, different frequencies may have induced diverse neurotransmitter release and then bringing different effects.[29]

However, there are several limitations to the present study. First, the gender differences of patients were not accounted for at the enrollment stage; Soh et al[30] have demonstrated that females are more sensitive to the analgesic effects of opioid than males. Consequently, variations in the dose-response rest with sex may have affected the sequential data. Second, the study population was limit to between 65 and 80 y undergoing spine surgery so the effect of TEAS on other ages or other types of surgeries should be considered carefully.

In conclusion, TEAS can enhance the efficacy of remifentanil on suppressing responses to tracheal extubation in elderly patients, the EC_{50} of remifentanil can reduce approximately 27% compared with group C.

Author contributions

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