

Multipoint transcutaneous electrical stimulation reduces median effective plasma concentration of propofol: A randomised clinical trial

Address for correspondence:

Dr. Feng Yi,
11 Xizhimen South Street
Xicheng District, Beijing, China.
E-mail: doctor_yifeng@sina.com

Zhang Jing, Yu Ling, Feng Yi

Department of Anaesthesiology, Peking University People's Hospital (Beijing Cancer Hospital), Beijing, China

Submitted: 07-Nov-2019

Revised: 04-Jan-2020

Accepted: 12-Mar-2020

Published: 01-Jun-2020

ABSTRACT

Background and Aims: Previous work shows that transcutaneous electrical stimulation (TES) has analgesic and sedative effects. However, it is unclear whether TES can affect the sedative effect of propofol or not. This study was designed to assess the effect of TES on median effective plasma concentration (Cp50) of propofol and haemodynamic changes before and after tracheal intubation. **Methods:** 48 patients belonging to ASA I or II posted for thyroidectomy were randomly allocated into control and TES groups. Up-and-down method was used to determine Cp50 of propofol. The average concentration of propofol in each crossover was calculated and the average concentration of those six values was defined as Cp50 of propofol. **Results:** Cp50 of propofol was $3.70 \pm 0.28 \mu\text{g/mL}$ and $3.08 \pm 0.31 \mu\text{g/mL}$ in control and TES groups, respectively ($P < 0.05$). There were no significant differences in MAP ($90.3 \pm 12.4 \text{ mmHg}$ vs. $97.0 \pm 10.8 \text{ mmHg}$, $94.2 \pm 18.7 \text{ mmHg}$ vs. $98.3 \pm 16.6 \text{ mmHg}$ and $84.9 \pm 14.1 \text{ mmHg}$ vs. $91.6 \pm 16.2 \text{ mmHg}$) and HR ($78.2 \pm 11.3 \text{ b/min}$ vs. $75.6 \pm 9.5 \text{ b/min}$, $90.9 \pm 15.4 \text{ b/min}$ vs. $90.4 \pm 14.9 \text{ b/min}$ and $86.7 \pm 13.7 \text{ b/min}$ vs. $84.0 \pm 15.9 \text{ b/min}$) at T0, T1 and T2 between two groups. In TES group, HR changes at T1 and T2 were significantly higher than those at T0. **Conclusion:** TES can make an assistant effect on sedation and decrease Cp50 of propofol. But the haemodynamic fluctuations in TES group, especially the HR changes, seem to be more obvious than those in control group.

Key words: Bispectral index, propofol, target-controlled infusion, transcutaneous electrical stimulation

Access this article online
Website: www.ijaweb.org
DOI: 10.4103/ija.IJA_775_19
Quick response code


INTRODUCTION

Transcutaneous electrical stimulation (TES), a non-invasive acupuncture technique, is similar to electroacupuncture in terms of fundamental principles. However, unlike electroacupuncture, TES avoids invasive procedure and is more conveniently performed than electroacupuncture. Furthermore, patients accept TES more readily than electroacupuncture. By stimulating special acupoints, TES causes the release of various mediators including endogenous opioids in the central nervous system, providing analgesic and sedative effects.^[1]

Neiguan (PC6) is a collateral point to Jueyin, the pericardium channel of hand. PC6 acupoint stimulation can modulate cardiovascular activity, an effect that may be attributed to the attenuation of

sympathoexcitatory cardiovascular reflex.^[2] Hegu (LI4) is a collateral point to Yangming, the large intestine channel of hand. When this acupoint is stimulated, Qi is taken up to ensure proper downward blood flow, which helps the body recover and reduce pain. In our previous work, stimulation of PC6 and LI4 acupoints was used to achieve sedation, analgesia and tranquilisation.^[3]

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Jing Z, Ling Y, Yi F. Multipoint transcutaneous electrical stimulation reduces median effective plasma concentration of propofol: A randomised clinical trial. *Indian J Anaesth* 2020;64:483-7.

In addition, the previous works have shown that TES has analgesic and sedative effects.^[4,5] A classical method to study the efficacy of drugs is to measure median effective plasma concentration (Cp50). To our best knowledge, however, there is no study having assessed the effect of TES on the Cp50 of propofol. Thus, the primary objective of this study was to determine whether multipoint TES performed on the LI4-PC6 acupoints could significantly reduce the Cp50 of propofol in patients undergoing thyroidectomy. The secondary objective was to find the influence of TES on haemodynamics.

METHODS

This was a prospective, single-blinded, randomised clinical trial aimed to find the Cp50 of propofol. This research was approved by the research ethics committees of Peking University People's Hospital, Beijing, China (No. 2013-09) and was registered in Chinese Clinical Trial Registry (Identifier: ChiCTR-TRC-14004435). Written informed consent was obtained from all patients.

This trial took a period from June 2014 to February 2015. Patients undergoing elective thyroidectomy were enrolled and they were assigned into two groups (control and TES groups) according to a random number. The group allocation numbers were concealed in sealed opaque envelopes that were opened after enrolment of the patients. Patients were blind to grouping because both groups received TES stimulation with different intensities. The inclusion criteria were normal thyroid function, aged 18–70 years, American Society of Anaesthesiologists (ASA) score I-II and BMI 17–30 kg/m². Patients with a history of severe circulatory or respiratory diseases, diabetes, long-term tranquilizer use, use of drugs that affect adrenal gland and sympathetic nerve functions, drug addiction and history of allergy to propofol were excluded.

After the patient entered the operation room, a peripheral venous catheter was placed and sodium lactate Ringer's solution was administered. The standard monitor was carried out with multifunctional monitor IntelliVue MP (Royal Philips Electronics company, Holland). The multipoint TES was performed with a HANS LH402 (HAN'S Acupoint Nerve Stimulator, Pukang medicine science and technology development company, Beijing, China). In control group, the electrodes were connected to the LI4 and PC6 acupoints on both sides 30 min before anaesthesia

induction with the minimum current intensity the patient could feel (frequency 2/100 Hz alternately). In TES group, the electrodes were connected to the LI4 and PC6 acupoints on both sides 30 min before anaesthesia induction with the maximum current intensity that the patient could tolerate (frequency 2/100 Hz alternately).

Patients in both groups received intravenous anaesthesia by target-controlled infusion (TCI) of propofol with a Graseby 3500 injection pump (Plasma target-controlled infusion mode, initial plasma concentration was 3 µg/mL, Graseby Medical company, UK). Up-and-down method was used to determine Cp50 of propofol. The initial plasma concentration of propofol was 3 µg/mL. Unconsciousness was defined as a BIS value less than 60. After the patient lost consciousness, BIS value was recorded every 30 s for 3 min, and the average value of these 6 data points was calculated. An average BIS value of 50 was considered as the cut-off for reducing or increasing the target propofol concentration. The gradient of the increase or decrease in the propofol plasma concentration was 0.3 µg/mL. If the average BIS value was less than 50 (positive), the initial target propofol concentration of the next patient was reduced by 0.3 µg/mL. If the average BIS value was higher than 50 (negative), the initial target propofol concentration of subsequent patient was increased by 0.3 µg/mL. When at least 6 independent alternations from negative to positive were observed, the test was terminated.

The induction process was same in both groups. We used target-controlled infusion (TCI) of propofol; the initial induction plasma concentration was 3 µg/mL. Three minutes after conscious disappeared (BIS < 60), fentanyl 1 µg/kg and rocuronium 0.6 mg/kg were given. After induction of general anaesthesia, oral intubation was performed using the direct laryngoscope. Continuous oxygen inhalation with mask was given before intubation to make sure the blood oxygen saturation was maintained above 95% during this process. After intubation, the lungs were mechanically ventilated with oxygen flow 2 L/min, tidal volume 8–10 mL/kg, frequency 10–12 times/min. Before operation, midazolam 0.03 mg/kg was given. Propofol, remifentanyl and rocuronium were used to maintain anaesthesia.

MAP, HR and BIS were recorded before TES (T0), 1 min after intubation (T1) and 3 min after intubation (T2). BIS values were also recorded every 30 s until 3 min after intubation.

SPSS 18.0 software was used for all statistical analysis. Normal distribution data were expressed as means ± SD. The *t*-test was used for intergroup comparison, while the Chi-square test was used for enumeration data.

According to the up-and-down method, the average concentration of propofol in each crossover from negative to positive was calculated and six average concentrations were obtained. Then, the average concentration of those six values was defined as Cp50 of propofol. The 95% confidence interval (CI) of Cp50 and the 95% effective plasma concentration of propofol (Cp95) were also calculated by Probit analysis.

One-way ANOVA was used to analyse the difference between T0 and the other time points. Repeated measurements were used to analyse the difference of the interaction effect between groups and time points. A value of *P* < 0.05 was considered statistically significant.

RESULTS

A total of 48 patients were enrolled and 10 were men. Control group included 23 patients and TES group included 25 patients. There were no statistical differences between groups in terms of sex, age, body mass index (BMI) or ASA status [Table 1].

The Cp50 of propofol was 3.70 ± 0.28 µg/mL (95% CI, 3.37–4.75) and 3.08 ± 0.31 µg/mL (95% CI, 2.56–3.68) in control and TES groups, respectively [Figure 1]. It was significantly decreased by 16.8% in the TES group (*P* = 0.004) [Figure 1]. The Cp95 was

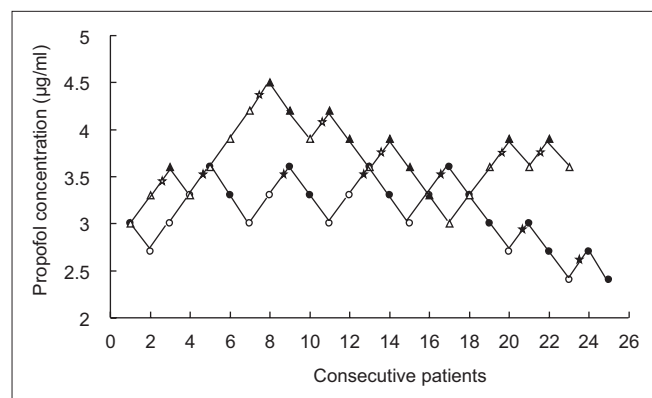


Figure 1: Induction plasma concentration of propofol and the results of average BIS value 5–8 min after unconsciousness in both groups. Control group: (▲) positive (average value of BIS was below 50), (△) negative (average value of BIS was not below 50), (☆) mean of crossover. TES group: (●) positive, (○) negative, (★) mean of crossover

4.64 µg/mL (95% CI 4.16–11.79) and 3.89 µg/mL (95% CI 3.48–10.23) in control and TES groups, respectively (*P* = 0.001).

Between the two groups, there were no significant differences in MAP and HR at T0, T1 and T2 [Table 2]. In control group, the differences of MAP and HR at T0, T1 and T2 were not significant. MAP of T1 increased by 4.4% compared with T0 and HR increased by 16.3%. In TES group, the differences of MAP at T0, T1 and T2 were not significant, but HR changes at T1 and T2 were significantly higher than those at T0 (*P* < 0.05). MAP of T1 increased by 1.3% compared with T0 and HR increased by 16.2%. Each group had 4 patients whose blood pressure elevated more than 20% after intubation. There were 11 cases whose heart rate elevated more than 20% after intubation in TES group. However, there were only 8 cases in control group.

DISCUSSION

This trial used BIS to monitor sedation depth and up-and-down method to quantitatively assess the effect of multipoint TES on LI4-PC6. The results showed that Cp50 of propofol in the TES group was 3.08 ± 0.31 µg/mL, which was 16.8% lower than that of control group, with a significant difference. Cp95 of propofol in the TES group was 3.89 µg/mL and was 16.2% lower than that of control group. Thus, the sedative effect of multipoint TES on LI4 and PC6 points of both sides for 30 min was equivalent to a plasma propofol concentration of 0.62 µg/mL. Therefore, our trial confirmed the sedation effect of TES. Meanwhile, TES may not strong enough to help inhibiting the haemodynamic reaction induced by intubation.

Table 1: The general data of patients

	Control Group (n=23)	TES Group (n=25)
Age ($\bar{x} \pm s$)	47.5 ± 11.9	48.2 ± 11.6
BMI1 ($\bar{x} \pm s$)	24.4 ± 3.1	24.3 ± 2.8
Sex (Male/Female)	5/18	5/20
ASA2 (I/II)	13/10	17/8

¹Body mass index. ²American Society of Anaesthesiologists

Table 2: MAP and HR in both groups ($\bar{x} \pm s$)

	T0	T1	T2
MAP (mmHg)			
Control Group (n=23)	90.3 ± 12.4	94.2 ± 18.7	84.9 ± 14.1
TES Group (n=25)	97.0 ± 10.8	98.3 ± 16.6	91.6 ± 16.2
HR (b/min)			
Control Group (n=23)	78.2 ± 11.3	90.9 ± 15.4	86.7 ± 13.7
TES Group (n=25)	75.6 ± 9.5	90.4 ± 14.9	84.0 ± 15.9

According to the previous study,^[6] a different-frequency electroacupuncture stimulation can cause a release of endogenous opioids and therefore produces different physiological and therapeutic effects. For instance, low-frequency stimulation induces analgesia effect through the release of β -endorphin, enkephalin and orphanin, meanwhile high-frequency stimulation induces analgesia effect through the release of dynorphin.^[7] The frequency of 2/100 Hz wave is often used alternately in thyroid operation.^[8] Therefore, a 2/100 Hz alternate wave was used in this trial.

The BIS is an ideal index for assessing the degree of cortex sedation. However, propofol seems to affect BIS faster than it affects systolic blood pressure.^[9] It has been shown that propofol titration with BIS monitoring during balanced anaesthesia can decrease propofol use and significantly improve recovery, indicating that BIS is valuable in guiding intraoperative propofol administration.^[10] BIS values between 40 and 60 indicate adequate general anaesthesia for surgery, and values below 40 indicate a deep hypnotic state.^[11] The previous study found that BIS value changes between 48 and 52 intraoperation^[12] could get satisfied sedation. The BIS value associated with 95% probability of loss of response to a stimulus was 46–48^[13] while the BIS value associated with 95% and 99% probability of loss of consciousness were 63 and 53, respectively.^[14] Thus, we chose BIS value at 50 as a target point to insure that patients were unresponsive to painful stimulus and maintained the BIS value 50 ± 5 intraoperation.

Our results indicated that multipoint TES on LI4 and PC6 points in both sides for 30 min before anaesthesia induction reduced the Cp50 and Cp95 of propofol. This suggests that the TES has a supplementary effect on sedation. TES has been proved to enhance the sedative effect of propofol, reduced the opioids consumption and reduced the incidence of anaesthesia-related side-effects.^[4,15] Electroacupuncture stimulation on PC6 has been reported to significantly deepen the sedation level of general anaesthesia.^[16]

The mechanism underlying the sedative effect of TES on LI4-PC6 is not clear. According to the theory of traditional Chinese medicine, Jingluo is a system of internal main and collateral channels, regarded as a network of energy passages. Acupuncture points are located in those channels. It is a complex system, which can balance the internal environment, reduce the threshold of sedative drug indirectly by weakening the excitability of a certain meridian. PC6 belongs to

pericardial meridian and often is used in cardiothoracic related aspects.^[17] LI4 belongs to large intestine meridian and sympathetic activity can be decreased when this acupoint is stimulated.^[18] We can acquire a sedative effect by stimulating both acupoints, but it is completely different from the mechanism causing by narcotic drugs. TES can subdue the excitement of a single meridian which would balance the internal body environment^[19] and can indirectly reduce the threshold of hypnotic sedatives.

For modern medicine, according to the available literatures, the mechanism of TES may be the secondary sedation effect of endogenous opioids.^[20] Other studies found evidences that TES or acupuncture could induce the changes of EEG activity. The activity of alpha and theta oscillations of EEG increased and decreased after TES.^[21,22] These results suggested that TES may modulate the activity and coherence of EEG to improve the sedation under anaesthesia.^[23]

In this trial, we confirmed that TES can produce a sedative effect and decrease Cp50 of propofol by 16.8%. As we know, TES also has a good auxiliary analgesic effect, but we found that the haemodynamic fluctuations in TES group, especially the HR changes, seem to be more obvious than those in control group. The differences of MAP at different time points were not significant, but HR changes at T1 and T2 were significantly higher than those at T0 in TES group. The previous studies also have similar results as our trial. One study^[24] approved that TES for 30 min before induction failed to inhibit the response of tracheal intubation. Other studies^[25,26] also showed that the application of TES can only partially reduce the haemodynamic changes during tracheal intubation. Hence, we may get the conclusion that although TES has a certain analgesic effect, it is not strong enough to inhibit intubation response. Besides, the dosage of propofol in TES group was decreased, which may also contribute to this result. Otherwise, the dosage of fentanyl was too small to inhibit the reaction of intubation. To inhibit the reaction of intubation, the dosage of fentanyl needs to reach 5–8 $\mu\text{g}/\text{kg}$.^[27] The dosage of fentanyl we used was 1 $\mu\text{g}/\text{kg}$ and lower than that of other experiments.^[25,28] This may also be one of the possible explanations.

CONCLUSION

In conclusion, this trial shows that multipoint TES at LI4 and PC6 can produce a sedative effect equivalent to a plasma propofol concentration of 0.62 $\mu\text{g}/\text{mL}$. It

indicates that multipoint TES may be useful to achieve non-invasive sedation, reduced dose of propofol. However, the analgesia effect is not strong enough to inhibit the haemodynamic changes induced by endotracheal intubation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

This study was supported by Major State Basic Research Development Program of China (973 Program, NO.2013CB531903).

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Yan YN, Li YL, Wu XY, Wang MX. The anesthesiologic value of transcutaneous acupoint electrical stimulation combined with general intravenous anesthesia in endoscopic thyroidectomy patients: A clinical study. *Chin J Integr Tradit West Med* 2014;34:545-8.
2. Wang G, Tian Y, Jia S, Zhou W, Zhang W. Pilot study of acupuncture point laterality: Evidence from heart rate variability. *Evid Based Complement Alternat Med* 2013;7:476064.
3. Litscher G, Wang L, Wang X, Gaischek I. Laser acupuncture: Two acupoints (Baihui, Neiguan) and two modalities of laser (658 nm, 405 nm) induce different effects in neurovegetative parameters. *Evid Based Complement Alternat Med* 2013;6:432764.
4. Wang H, Xie Y, Zhang Q, Xu N, Zhong H, Dong H, *et al.* Transcutaneous electric acupoint stimulation reduces intra-operative remifentanyl consumption and alleviates postoperative side-effects in patients undergoing sinusotomy: A prospective, randomized, placebo-controlled trial. *Br J Anaesth* 2014;112:1075-82.
5. Liu X, Li SQ, Wang BG, An L, Ren X, Wu H. Intraoperative and postoperative anaesthetic and analgesic effect of multipoint transcutaneous electrical acupuncture stimulation combined with sufentanil anaesthesia in patients undergoing supratentorial craniotomy. *Acupunct Med* 2015;33:270-6.
6. Han JS. New evidence to substantiate the frequency specificity of acupuncture-induced analgesia. *Acupunct Res* 2001;26:224-7.
7. Lin JG, Chen WL. Acupuncture analgesia: A review of its mechanisms of actions. *Am J Chin Med* 2008;36:635-45.
8. Zhang SY, Gao YQ, Jia Q. Thyroid operative skills under acupuncture anesthesia. *J Clin Acupunct Moxibustion* 2012;28:74-6.
9. Kazama T, Ikeda K, Morita K, Kikura M, Doi M, Ikeda T, *et al.* Comparison of the effect-site $k_{(e)O}$ s of propofol for blood pressure and EEG bispectral index in elderly and younger patients. *Anesthesiology* 1999;90:1517-27.
10. Gan TJ, Glass PS, Windsor A, Kikura M, Doi M, Ikeda T, *et al.* Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. BIS Utility Study Group. *Anesthesiology* 1997;87:808-15.
11. Avidan MS, Zhang L, Burnside BA. Anesthesia awareness and the bispectral index. *N Engl J Med* 2008;358:1097-108.
12. Chen XX, Yang R, Tu J. Clinical application of bispectral index in general anesthesia. *J Ningxia Med Coll* 2002;24:400-2.
13. Yang N, Zuo MZ, Yue Y. Comparison of C50 for propofol-remifentanyl target-controlled infusion and bispectral index at loss of consciousness and response to painful stimulus in elderly and young patients. *Chinese Med J* 2015;128:1994-9.
14. Iannuzzi M, Iannuzzi E, Rossi F, Berrino L, Chieffari M. Relationship between bispectral index, electroencephalographic state entropy and effect-site EC50 for propofol at different clinical endpoints. *Br J Anaesth* 2005;94:613-6.
15. Nayak S, Wenstone R, Jones A, Nolan J, Strong A, Carson J. Surface electrostimulation of acupuncture points for sedation of critically ill patients in the intensive care unit—A pilot study. *Acupunct Med* 2008;26:1-7.
16. Chen Y, Zhang H, Tang T, Shu J. Impact of bilateral ST36 and PC6 electroacupuncture on the depth of sedation in general anesthesia. *Acupunct Med* 2015;33:103-9.
17. Jia Q, Shi JH, Gao YQ. Thyroid operation by acupuncture anesthesia: Research progress in the past decade. *J Clin Acupunct Moxibustion* 2011;23:59-61.
18. Hsiu H, Hsu WC, Hsu CL, Huang SM. Assessing the effects of acupuncture by comparing needling the Hegu acupoint and needling nearby nonacupoints by spectral analysis of microcirculatory laser Doppler signals. *Evid Based Complement Alternat Med* 2011;2011:435928.
19. Uchida S, Hotta H. Acupuncture affects regional bloodflow in various organs. *Evid Based Complement Alternat Med* 2008;5:145-51.
20. Biella G, Sotgiu ML, Pellegata G, Paulesu E, Castiglioni I, Fazio F. Acupuncture produces central activations in pain regions. *Neuroimage* 2001;14:60-6.
21. Hsu SF, Chen CY, Ke MD, Huang CH, Sun YT, Lin JG. Variations of brain activities of acupuncture to TE5 of left hand in normal subjects. *Am J Chin Med* 2011;39:673-86.
22. Chen AC, Liu FJ, Wang L, Arendt-Nielsen L. Mode and site of acupuncture modulation in the human brain: 3D (124-ch) EEG power spectrum mapping and source imaging. *Neuroimage* 2006;29:1080-91.
23. Liu X, Wang J, Wang BQ, Wang YH, Teng Q, Yan J, *et al.* Effect of transcutaneous acupoint electrical stimulation on propofol sedation: An electroencephalogram analysis of patients undergoing pituitary adenomas resection. *BMC Complement Alternat Med* 2016;16:33.
24. Wang MS, Chen HL, Bi YL. The strengthening effect of transcutaneous electrical acupoint stimulation on total intravenous anesthesia with propofol (Chinese). *J Clin Anesth* 2008;8:726-8.
25. Shi JH, Gao YQ, Li Y, Bi YL. Electroacupuncture for prevention of the intratracheal intubation stress response in general anesthesia. *Chin Acupunct Moxibustion* 2008;24:1.
26. Ma FG, Wang MS, Chen HL. Effect of transcutaneous electrical acupoint stimulation on bispectral index and stress reaction in patients undergo tracheal intubation. *ACTA Acad Med Qing Dao Univ* 2009;8:374-6.
27. Chokshi T, Channabasappa S, Vergheese DC, Bajwa SJ, Gupta B, Mehdiratta L. Re-emergence of TIVA in COVID times. *Indian J Anaesth* 2020;64, Suppl S2:125-31.
28. Yu HC, Geng WJ, Tang HL. Preventive effect of transcutaneous electro-acupuncture on the intratracheal extubation stress response in general anesthesia of patients with breast cancer undergoing modified radical mastectomy. *Chin J Integr Tradit West Med* 2009;11:990-2.