

Effects of transcutaneous acupoint electrical stimulation combined with low-dose sufentanil pretreatment on the incidence and severity of etomidate-induced myoclonus

A randomized controlled trial

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Abstract

Background: Myoclonus is an undesirable phenomenon that occurs after induction of general anesthesia using etomidate. Opioids such as sufentanil are considered effective pretreatment drugs for myoclonus inhibition, although high doses are required. Transcutaneous acupoint electrical stimulation (TAES), a noninvasive technique involving electrical stimulation of the skin at the acupuncture points, exhibits analgesic effects, promotes anesthetic effects, decreases the dose of anesthetic drugs, and increases endogenous opioid peptide levels. In the present study, we investigated the effects of TAES combined with low-dose sufentanil pretreatment on the incidence and severity of etomidate-induced myoclonus in patients undergoing elective hysteroscopy.

Methods: In a double-blind manner, 172 patients (American Society of Anesthesiologists class I–II; age, 20–55 years) scheduled to undergo elective hysteroscopy were randomized into the following groups (n=43 each): control (false TAES followed by saline injection after 30min), TAES (TAES followed by saline injection after 30minutes), sufentanil [false TAES followed by low-dose sufentanil (0.1 µg/kg) injection after 30 minutes], and sufentanil plus TAES (TAES followed by low-dose sufentanil injection after 30 minutes). In all groups, general anesthesia was induced by etomidate 0.3 mg/kg after sufentanil or saline injection. The incidence and severity of myoclonus were assessed for 2 minutes after etomidate administration. The visual analogue scale (VAS) scores for pain at 1 hour after surgery were recorded. The heart rate (HR), mean arterial pressure (MAP), and peripheral capillary oxygen saturation (SPO₂) were recorded before premedication, after etomidate injection, after uterus expansion, and after recovery from anesthesia.

Results: The incidence of myoclonus was highest in the control group (88.3%), followed by TAES (74.4%), sufentanil (60.4%), and TAES plus sufentanil (48.8%) groups. Thus, the incidence was significantly higher in the control and TAES groups than in the sufentanil and TAES plus sufentanil groups. Grade 3 myoclonus occurred in 30.2%, 9.3%, 11.6%, and 9.3% patients in the control, TAES, sufentanil, and TAES plus sufentanil groups, respectively, with significant differences between the control group and the other 3 groups. Furthermore, the postoperative VAS scores for pain were significantly lower in the TAES, sufentanil, and TAES plus

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sufentanil groups compared with those in the control group. There were no significant differences in any other parameters among groups.

Conclusion: Our results suggest that TAES combined with low-dose opioids such as sufentanil can decrease the incidence and severity of etomidate-induced myoclonus.

Abbreviations: AES = acupoint electrical stimulation, GABAA = gamma-aminobutyric acid type A, HR = heart rate, L14 = the acupoint hegu, MAP = mean arterial pressure, NIBP = noninvasive blood pressure, SJ5 = the acupoint waiguan, SPO₂ = peripheral capillary oxygen saturation, TAES = transcutaneous acupoint electrical stimulation, VAS = the visual analogue scale.

Keywords: etomidate, hysteroscopy, myoclonus, sufentanil, transcutaneous acupoint electrical stimulation

1. Introduction

Since the introduction of etomidate as an agent for the induction of general anesthesia in 1973,^[1] its use has gained popularity because of a favorable cardiovascular profile,^[2–4] minimal respiratory side effects,^[5] and rapid onset of action and clearance from the body.^[6] Etomidate is a common choice of anesthetic drug for procedures that cause short-term pain, particularly in hemodynamically compromised patients.^[7] However, pain on injection and myoclonus are 2 well-known and undesirable side effects, although the former is now minimized by a new lipid formulation of etomidate, known as (etomidate-lipuro).^[8] On the other hand, etomidate-induced myoclonus remains a serious clinical problem, with an incidence of 50% to 80% in patients who do not receive premedication.^[9,10] Unfortunately, the underlying mechanism for this side effect remains unknown. Myoclonus is a clinically significant side effect that can result in regurgitation and aspiration in patients undergoing emergency surgery without fasting.^[9] It is also detrimental for patients with open globe injuries or limited cardiovascular reserves, because it can increase the intraocular pressure and restrict cardiac function.^[11] Several pretreatment drugs for the inhibition of myoclonus have been investigated, including benzodiazepines,^[12,13] opioids,^[14–18] and muscle relaxants,^[19,20] and all have the ability to prevent this side effect to some extent. Of these, opioids are the most effective, albeit at high doses, which can cause undesirable adverse effects such as sedation, cough, apnea, respiratory depression, and chest wall rigidity.^[17,21,22] Sufentanil is considered an effective clinical opioid analgesic for inhibiting the myoclonus induced by etomidate.^[23] For minor surgeries such as elective hysteroscopy, where the average time at site is always 20 to 30 min, benzodiazepines and muscle relaxants cause a significant delay in the recovery from anesthesia. Therefore, the ideal pretreatment drug for preventing myoclonic movements without significant side effects has not yet been identified.

Acupoint electrical stimulation (AES), a classical procedure under Traditional Chinese Medicine, combined with pretreatment drugs is currently an exciting area of research. Transcutaneous AES (TAES) is an improved treatment method used in the practice of acupuncture. Thus, acupuncture and AES are methodologically the same. Transcutaneous AES (TAES) is a noninvasive, safe, and simple technique involving electrical stimulation of skin over acupuncture points. Transcutaneous AES exhibits analgesic effects, promotes anesthetic effects, and reduces the dose of anesthetic drugs.^[24,25] Furthermore, it increases the levels of endogenous opioid peptides, such as enkephalin, beta-endorphin, and dynorphin, which produce the same effects as those with opioids.^[26]

The acupoint hegu (L14) is located in the web between the thumb and first finger on the back of the hand, at the mid-

metacarpal level. The acupoint waiguan (SJ5) is located on the posterior forearm, between the radius and ulna, on the radial side of the extensor digitorum communis tendons, 2 inches proximal from the wrist. Hegu (L14), the most widely treated acupoint, inhibits involuntary contraction of the diaphragm and is used in the treatment of hiccups. Hegu (L14) is also involved in mood stabilization and is helpful in alleviating preoperative stress in patients. Further, this acupoint has an analgesic effect that is useful in treating headache and toothache. In contrast, the main use of waiguan (SJ5) is in the treatment of headache, shoulder pain, intercostal pain, and tremors of the feet. We chose hegu (L14) and waiguan (SJ5) as the 2 acupoints for pretreatment of etomidate-induced myoclonus in this study.

We investigated the effects of TAES combined with low-dose sufentanil pretreatment on the incidence and severity of myoclonus induced by etomidate in patients undergoing elective hysteroscopy. Transcutaneous AES is commonly used alone as a complimentary treatment for the management of pain, particularly acute postoperative pain^[27] and chronic pain.^[28] We hypothesized that in combination with intravenous sufentanil, TAES would decrease myoclonus following administration of induction doses of etomidate.

2. Methods

This study was approved by the Ethics Committee of Wenzhou Medical University (clinical trial number: ChiCTR-INR-16009084; Registry URL: YJLCYJ-2016-168). This manuscript adheres to the applicable Equator guidelines. Patients scheduled for elective hysteroscopy (American Society of Anesthesiologists class I–II; age, 20–55 years) were included. All patients provided written informed consent for participation in the study. The exclusion criteria were as follows: presence of incisions, scars, or skin infection at the hegu and waiguan acupoints; history of allergy to drugs used in the study; history of spinal surgery; sinus bradycardia; severe neurological diseases; severe respiratory diseases; severe cardiovascular diseases; and any other diseases that required exclusion. None of the patients received premedication.

On arrival in the operating room, standard monitors, including those for electrocardiography, heart rate, noninvasive blood pressure (NIBP), and peripheral capillary oxygen saturation (SpO₂), were attached to the patient, and to ensure patient safety, monitoring was continued until the end of the operation. A 22-gauge cannula was inserted into the dorsum of the patient's hand for drug administration. Oxygen was supplied with a non-rebreathing mask and reservoir system with an oxygen flow of 3 L/min.

All patients were randomized in a double-blinded manner to 1 of 4 pretreatment groups (n = 43 each): control, TAES, sufentanil, and sufentanil plus TAES.

2.1. Control group

The patients received false TAES (2/100Hz; dilatational waves), bilaterally, at the hegu and waiguan acupoints. The selected intensity was the least value at which the patient could feel the stimulation. Intravenous saline (2mL) was administered 30 minutes after false TAES, following which anesthesia was induced with 0.3mg/kg etomidate (En Pharmaceutical Co Ltd, Jiangsu).

2.2. TAES group

The patients received TAES (2/100Hz; dilatational waves) bilaterally, at the hegu and waiguan acupoints for 30 minutes. The selected intensity was the patient's maximum tolerated current value minus 1mA. Intravenous saline (2mL) was administered 30 minutes after TAES, following which anesthesia was induced with 0.3 mg/kg etomidate.

2.3. Sufentanil group

The patients received false TAES, as described for the control group. Intravenous sufentanil (EuroCept B.V) 0.1 µg/kg (diluted to 2 mL) was administered 30 minutes after false TAES, following which anesthesia was induced with 0.3 mg/kg etomidate.

2.4. Sufentanil plus TAES group

The patients received TAES (2/100Hz; dilatational waves) bilaterally at the hegu and waiguan acupoints for 30 minutes. The selected intensity was the patient's maximum tolerated current value minus 1mA. Intravenous sufentanil 0.1 µg/kg (diluted to 2 mL) was administered 30 minutes after TAES, following which anesthesia was induced with 0.3 mg/kg etomidate.

The incidence and severity of myoclonus were assessed for 2 minutes after etomidate administration. A physician blinded to the treatment assessed myoclonus. The clinical grades of myoclonus were assigned as follows: 0, no myoclonus; 1, mild myoclonus (short movements of a body part, such as the wrist or a finger); 2, moderate myoclonus (mild movements of 2 different muscles, such as those in the face and leg); and 3, severe myoclonus (intense clonic movements of 2 or more muscle groups, e.g., fast abduction of a limb).^[10] No other drugs were used between the pretreatment drug and at the end of induction.

After the 2-minute assessment period, propofol (Astrazeneca Pharmaceutical Co Ltd, London, England) 0.1 mg/(kg·min) and remifentanil (Yichang Pharmaceutical Co Ltd) 0.1 µg/(kg·min) were administered to maintain comfortable anesthesia until 3 minutes before the completion of surgery. In case the patient moved or frowned during surgery, propofol was added at 0.5 to 1 mg/kg. If respiratory depression developed (breathing rate <8/min or oxygen saturation <90%), artificial positive pressure

ventilation was adopted. If the systolic blood pressure was <90 mm Hg or the diastolic blood pressure was <60 mm Hg, ephedrine 5 to 10 mg was administered. If the heart rate (HR) was <50 beats/min, atropine 0.5 mg was administered.

The visual analogue scale (VAS) score for pain at 1 hour after surgery was recorded for all patients. In addition, HR, mean arterial pressure (MAP), and SPO₂ were recorded before premedication (T1), after etomidate injection (T2), after uterus expansion (T3), and after recovery from anesthesia (T4). Finally, all related adverse reactions, including pain on injection, respiratory depression, intraoperative movements, and postoperative nausea and vomiting, among others, were documented for all patients.

2.5. Statistical analysis

We used a randomization table generated by a computer to allocate the patients into 4 groups (n = 43 per group)—the control group, TAES group, sufentanil group, and sufentanil plus TAES group—to detect differences in the incidence and severity of myoclonus, which were determined by an independent staff member. After obtaining consent from the patients and their families, every patient received TAES (or false TAES) before the surgery. The anesthetist involved in the surgery, who was blinded to the purpose of this study, prepared the same anesthetic based on the patient's weight. Another member, who was blinded to the patient's group, evaluated the clinical parameters of the patients during and after the surgery to collect data.

All statistical analyses were performed with SPSS 13 software (Statistical Product and Service Solutions, SPSS Company). Continuous values are expressed as means ± standard deviations. Intergroup differences were analyzed using one-way analysis of variance (ANOVA). Count data were compared using χ^2 tests, and hierarchical data were compared using nonparametric Kruskal–Wallis tests. If differences were observed, Nemenyi tests were used. A *P* value <.05 was considered statistically significant. The datasets generated and analyzed during the current study are available from the corresponding author on request.

3. Results

There were no significant differences in patient characteristics among groups (Table 1, *P* > .05).

The incidence of myoclonus was the highest in the control group (88.3%), followed by the TAES (74.4%), sufentanil (60.4%), and sufentanil plus TAES (48.8%) groups. Moreover, the incidence of grade 3 myoclonus was 30.2% in the control group, 9.3% in the TAES group, 11.6% in the sufentanil group, and 9.3% in the TAES plus sufentanil group. Although the incidence of myoclonus was not significantly different between the control and TAES groups, the incidence of severe

Table 1

Characteristics of control patients and patients who received transcutaneous acupoint electrical stimulation (TAES) and/or low-dose sufentanil pretreatment before etomidate injection.

Group	Age (years)	Height (cm)	Weight (kg)	Body mass index (kg/m ²)
Control	33.2 ± 6.9	158.5 ± 4.3	54.8 ± 8.0	21.7 ± 2.9
TAES	35.4 ± 7.5	158.1 ± 5.0	52.6 ± 8.2	20.9 ± 2.7
Sufentanil	34.3 ± 8.3	157.8 ± 3.3	53.9 ± 7.6	21.6 ± 2.7
Sufentanil plus TAES	35.4 ± 8.0	158.3 ± 4.2	53.7 ± 5.7	21.3 ± 2.0

P > .05 vs. control group.

Table 2

Incidence and severity of myoclonus after etomidate injection in control patients and patients who received transcutaneous acupoint electrical stimulation (TAES) and/or low-dose sufentanil pretreatment before etomidate injection.

Group	Myoclonus grade				Overall incidence of myoclonus (%)	Incidence of grade 3 myoclonus (%)
	0	1	2	3		
Control	5	13	12	13	88.3	30.2
TAES	11	14	14	4	74.4	9.3*
Sufentanil	17	12	9	5	60.4*	11.6*
Sufentanil plus TAES	22	10	7	4	48.8†	9.3*

* $P < .05$ vs. control group.

† $P < .01$ vs. control group.

Table 3

Time to emergence from anesthesia, visual analogue scale (VAS) score for pain at 1 h after surgery, and incidence of adverse reactions in control patients and patients who received transcutaneous acupoint electrical stimulation (TAES) and/or low-dose sufentanil pretreatment before etomidate injection.

Group	VAS score	Pain on injection	Intraoperative movements	Respiratory depression	Vomiting
Control	2.9 ± 0.6	1	5	5	1
TAES	1.6 ± 1.1*	0	3	3	2
Sufentanil	3.3 ± 1.0	2	6	7	2
Sufentanil plus TAES	1.6 ± 1.2*	2	4	7	0

* $P < .05$ vs. control group.

myoclonus was significantly lower in the latter than in the former ($P < .05$). In addition, the incidence and severity of myoclonus were significantly lower in the sufentanil ($P < .05$) and sufentanil plus TAES ($P < .01$) groups than in the control group (Table 2).

The VAS score for pain at 1 h after surgery was significantly lower in the TAES and sufentanil plus TAES ($P < .05$) groups than in the control group. The incidence of adverse effects was low and similar among groups (Table 3). HR and SPO₂ values were not significantly different among the 4 time points ($P > .05$). However, MAP values at T3 and T4 were significantly lower in the sufentanil and sufentanil plus TAES groups than in the control group ($P < .05$). In the sufentanil group and sufentanil plus TAES group, MAP at T3 and T4 was significantly lower than that in the TAES group ($P < .05$). In the sufentanil plus TAES

group, MAP was significantly lower at T3 and T4 than at T2 ($P < .05$; Table 4).

4. Discussion

We investigated the effects of TAES combined with low-dose sufentanil pretreatment on the incidence and severity of myoclonus induced by etomidate in patients undergoing elective hysteroscopy. The results showed that TAES and sufentanil exerted synergistic effects and significantly decreased the incidence and severity of myoclonus induced by etomidate. In fact, TAES alone was effective in decreasing the severity of myoclonus. Most importantly, no adverse effects were observed, with a remarkable decrease in the VAS score for pain in the TAES and TAES plus sufentanil groups. Finally, as suggested in Table 4,

Table 4

Mean arterial pressure (MAP), heart rate (HR), and peripheral capillary oxygen saturation (SPO₂) before premedication (T1), after etomidate injection (T2), after uterus expansion (T3), and after recovery from anesthesia (T4) in control patients and patients who received transcutaneous acupoint electrical stimulation (TAES) and/or low-dose sufentanil pretreatment before etomidate injection.

Group	T1	T2	T3	T4	
MAP (mm Hg)	Control	98.9 ± 12.9	91.3 ± 9.8	88.3 ± 10.7	93.0 ± 9.8
	TAES	97.0 ± 11.0	90.6 ± 12.6	90.2 ± 11.9	91.2 ± 10.7
	Sufentanil	101.4 ± 14.1	88.5 ± 12.6	83.6 ± 10.2*†	85.6 ± 9.4*†
	Sufentanil plus TAES	100.8 ± 15.4	85.1 ± 12.8	77.9 ± 11.3*†‡	79.7 ± 11.5*†‡
HR (/min)	Control	71.5 ± 11.0	66.2 ± 9.3	80.7 ± 14.6	69.5 ± 9.5
	TAES	69.0 ± 11.9	66.5 ± 12.2	76.1 ± 11.7	72.1 ± 12.5
	Sufentanil	71.3 ± 13.1	65.9 ± 11.4	79.3 ± 13.4	70.6 ± 10.4
	Sufentanil plus TAES	69.6 ± 9.8	65.1 ± 9.0	74.6 ± 12.2	69.7 ± 10.3
SpO ₂ (%)	Control	99.2 ± 1.0	99.2 ± 1.4	99.6 ± 0.7	99.5 ± 0.7
	TAES	99.3 ± 1.0	99.5 ± 0.7	99.3 ± 1.2	99.3 ± 0.8
	Sufentanil	99.1 ± 1.1	99.3 ± 1.2	99.3 ± 1.5	99.2 ± 1.2
	Sufentanil plus TAES	99.5 ± 0.7	99.6 ± 0.6	99.5 ± 0.7	99.5 ± 0.8

* $P < .05$ vs. control group.

† $P < .05$ vs. TAES group.

‡ $P < .05$ vs. T2.

even small doses of sufentanil (0.1 µg/kg) could visibly influence the hemodynamics of the patient. Collectively, our findings provide evidence that TAES is a valuable treatment.

Etomidate has been commonly used for hemodynamically unstable patients, short-term anesthesia, and rapid sequence intubation owing to multiple advantages including rapid onset of action, favorable cardiovascular profile, minimal respiratory and intracranial pressure, and nervous system protection.^[1–6,29] However, etomidate-induced myoclonus remains a clinically significant side effect with severe consequences such as vitreous prolapse in a patient with open eye injury,^[11] ECG lead detachment with a decrease in oxygen saturation,^[30] muscle pain, higher energy consumption and serum potassium levels, higher internal gastric pressure, regurgitation and aspiration.

Etomidate interacts with gamma-aminobutyric acid type A (GABAA) receptors, although the precise mechanism underlying myoclonus caused by this drug is unknown. Doenicke et al^[9] conducted an electroencephalogram study and reported that myoclonus induced by etomidate is attributed to subcortical disinhibition, similar to that causing restless leg syndrome during normal human sleep, and is not related to epileptic foci. Another study reported that the depression of inhibitory circuits earlier than that of excitatory neuronal circuits after etomidate administration could be the reason,^[31] while yet another study reported that the interruption of GABA neurons increases the sensitivity of skeletal muscle-associated pathways, leading to spontaneous nerve transmissions and, consequently, myoclonus.^[32]

An ideal drug for the inhibition of etomidate-induced myoclonus is one that should not interfere with the favorable pharmacodynamic profile of etomidate or cause any undesired side effects. Although several drugs have been investigated from this perspective, their results are inconclusive.

Benzodiazepines^[12,13,33] can decrease myoclonic movements to some extent, although it results in moderate hemodynamic side effects and prolonged recovery. Myoclonus inhibition by opioids is dose-dependent. Several studies have evaluated the effectiveness of opioids (fentanyl, sufentanil, and remifentanyl) for the inhibition of myoclonus^[14–18,22] and have reported that high doses are required for complete inhibition. However, these high doses result in significant side effects such as sedation, cough, apnea, respiratory depression, and chest wall rigidity.^[21] While rocuronium^[19,20] causes muscle relaxation and significantly decreases the frequency of myoclonus, it also results in airway obstruction, regurgitation, and aspiration. During long surgeries, all the above-mentioned disadvantages can be dealt by the anesthetist, whereas they create problems during short surgeries. AES was developed under a special national condition in China during the 1950s to 1970s. The main mechanism of acupuncture can be explained by 3 different pathways: local nerve excitement, pain signal collision, and endorphin secretion. Acupuncture anesthesia was initiated in 1958, and, reflecting the historical background of China after the 1960s, the use of this technique widely spread throughout the country. It extended to other countries after 1971, creating a significant impact and garnering attention from medical academia worldwide.^[34]

While conventional acupuncture requires the insertion of needles at acupoints, TAES is a noninvasive, safe, and simple technique involving electrical stimulation of the skin over these acupoints. According to the principles of Traditional Chinese Medicine, the human body comprises several collaterals and over 700 hundred acupoints, with each one serving a different function. Stimulation of the hegu and waiguan acupoints contributes to sedation and analgesia.

While low-dose sufentanil results in fewer side effects, it cannot efficiently inhibit myoclonus. In the present study, we investigated the effects of low-dose sufentanil in combination with TAES and found a marked decrease in the incidence and severity of myoclonus induced by etomidate, which is a clinically significant finding. In addition, we found that the incidences of intraoperative movements and respiratory depression were the lowest in the TAES group, which indicates that TAES can accelerate awakening and strengthen the sedation and analgesic effects without causing respiratory depression. Low-dose (0.1 µg/kg) sufentanil also decreased the incidence and severity of etomidate-induced myoclonus when administered alone. Although the incidence of respiratory depression was high with sufentanil alone and in combination with TAES, the effects were transient and clinically insignificant. The incidence of myoclonus in the control group was 88%, which is higher than that (50%–80%) reported in previous studies.^[9,33] This could be attributed to the longer assessment time in our study (2 minutes) compared to that in previous studies (1 minute). The incidence of myoclonus was the highest at 30 to 60 seconds after etomidate injection, but we considered that assessment for 2 minutes was more appropriate, in case myoclonus developed after 1 minute. Thus, extension of the observation period increased the reliability of our study findings.

Our study has a few limitations. The first and the most important one is that all patients were women of child-bearing age. According to previous studies, male patients are more likely to develop myoclonus than female patients, with children aged 5 to 10 years comprising the most susceptible population (90.2%).^[35,36] Second, only the incidence and severity of myoclonus was assessed in the present study, and the durations of myoclonic movements were not recorded. Third, because propofol and remifentanyl were required to maintain comfortable anesthesia until 3 minutes before the completion of surgery, the precise effects of TAES plus sufentanil on short-term recovery could not be assessed. Further studies are needed to address these limitations.

5. Conclusions

The results of our study indicate that TAES combined with low-dose sufentanil pretreatment significantly decreases the incidence and severity of myoclonus induced by etomidate administered for the induction of anesthesia, with minimal adverse effects. While TAES was found to be an effective treatment for etomidate-induced myoclonus, it was more effective in combination with low-dose sufentanil. This strategy not only decreases the dose of drugs used but also minimizes side effects, thus providing a safer and more comfortable medical model. We believe that TAES has several additional functions and advantages that remain undiscovered, and the introduction of TAES for clinical indications is expected in the future.

Author contributions

YL designed and performed the experiment; wrote the manuscript. HH designed the experiment. JX performed data collection and analysis. WJ performed the experiment.

CJS implemented the experiment. YP implemented the experiment. LW implemented the experiment. YM designed the experiment. QD, WG, JW provided financial and technical support.

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