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Effects of cranial electrotherapy stimulation on preoperative anxiety, pain and endocrine response

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Abstract

Objectives: Cranial electrotherapy stimulation (CES) is used as a treatment for depression and anxiety, and as an adjunctive intervention for pain management. This prospective study investigated whether CES could decrease preoperative anxiety, the injection pain of rocuronium, postoperative pain and stress hormone levels.

Methods: Female patients undergoing thyroidectomy were randomly assigned to two groups, to receive either no pretreatment (control group) or CES pretreatment. Anxiety score, withdrawal response on rocuronium injection, and pain scores at 1, 4, 12 and 24 h post surgery were evaluated. Adrenocorticotrophic hormone (ACTH), cortisol and glucose levels were measured. Patients were blinded to the treatment condition.

Results: Fifty patients entered the study ($n = 25$ per group). Anxiety score and withdrawal responses during rocuronium injection were significantly reduced in the CES group compared with the control group. Pain score was significantly lower in the CES group than in the control group, 1 h and 4 h post surgery. There were no significant differences in ACTH, cortisol and glucose levels.

Conclusions: CES pretreatment appears to reduce the level of preoperative anxiety, injection pain of rocuronium and postoperative pain. However, CES pretreatment did not affect stress hormone responses.

Keywords

Adrenocorticotrophic hormone, anxiety, cortisol, cranial electrotherapy stimulation, postoperative pain

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Introduction

Cranial electrotherapy stimulation (CES) is a nondrug treatment approach with effects that include improvements in anxiety, depression, insomnia and stress.[1] CES has been used for pain relief in patients with chronic pain syndromes such as headache, lower back pain, toothache and fibromyalgia.[1] It may work by elevating the pain threshold, due to its stress-reducing effects, when anxiety and depression are reduced below clinical levels.[1] Kim et al.[2] reported that CES pretreatment reduced the level of preoperative anxiety and haemodynamic responses in patients undergoing surgery.

Two-thirds of patients scheduled for anaesthesia and surgery are likely to experience various types of anxiety or fear about anaesthesia, pain, postoperative prognosis, survival and death.[3] Increased preoperative anxiety can cause postoperative psychological complications and is associated with lengthened periods of hospital stay and recovery.[4] The stress due to anaesthesia and surgery is associated with activation of the hypothalamus–pituitary–adrenal gland (HPA) axis and an increase in circulating blood adrenocorticotrophic hormone (ACTH).[5–7] Increased cortisol concentrations have been observed in all types of surgery and may lead to an increase in blood glucose levels.[5] Such hormone metabolism reactions depend on the degree and time of surgical stimulation, the patient's age and the methods of anaesthesia and surgery used.[6,7]

Various medications (particularly benzodiazepam derivatives such as midazolam, lorazepam or diazepam, and opioids) are used for relieving preoperative anxiety or intraoperative and postoperative pain reduction, and are likely to trigger residual sedative actions or adverse effects on the respiratory and cardiovascular systems.[8] CES is a method which does not have such adverse effects; as it is performed on patients before surgery it might ensure anaesthetic induction with a potentially better safety profile, compared with medical therapy use. Clinically, when patients exhibit a severe preoperative anxiety state or have a risk factor for sedatives, anaesthesiologists can use CES pretreatment (with or without pharmacological premedication) on the day before surgery and on the day of surgery itself, to reduce preoperative anxiety and postoperative pain.[2,9]

The present study investigated the effects of CES on preoperative anxiety, withdrawal response during injection of rocuronium and postoperative pain and on stress hormone levels.

Patients and methods

Patients

This prospective study was carried out at the Department of Anesthesiology and Pain Medicine, Ansan Hospital of Korea University College of Medicine between 1st February 2010 and 30th September 2010. The study was approved by the Institutional Review Board of Ansan Hospital. Written, informed consent to participate in this study was obtained from all patients.

Female patients aged 20–65 years old with American Society of Anesthesiologists (ASA) Physical Status Classification I or II, who were scheduled for thyroidectomy for suspected thyroid cancer, were included in the study. Exclusion criteria were: age >65 years, serious renal disease, body mass index ≥ 25, pregnancy, endocrine or neuromuscular disease, cardiac pacemaker and psychiatric medications. Patients were randomized to either the control group or the CES group by computer-generated random numbering.

Clinical evaluations and data collection

Cranial electrotherapy stimulation was performed in patients between 20:00 h and 22:00 h on the day before surgery, and

between 07:00 h and 09:00 h on the day of surgery. Treatment was performed for 20 min. All treatments were given via electrodes that were clipped to the patients' ear lobes. A Microcurrent Cranial Electrotherapy Stimulator (Alpha-Stim® 100, Electromedical Products International, Mineral Wells, Texas, USA) was used and was preset to provide microcurrents (100 μA, 0.5 Hz) for 20 min. The control group was given identical ear clip electrodes to the study group, but the current was not given. All patients, hospital staff and the examining physician remained blind to the treatment condition. Anxiety level was assessed subjectively by the patient, using a five-point Likert scale[10] where '1' indicated no anxiety, '2' indicated slightly anxious, '3' indicated moderate anxiety, '4' indicated a lot of anxiety and '5' indicated extremely anxious.

Patients were premedicated with an intramuscular injection of 0.2 mg of glycopyrrolate 30 min before anaesthesia. Anaesthesia was induced using propofol 2 mg/kg intravenous (i.v.) injection, followed by slow infusion of rocuronium 0.6 mg/kg i.v. over 5 s, after the patient had lost consciousness. Anaesthesia was maintained with N_2O 1.5 l/min-O_2 1.5 l/min and sevoflurane 1.5–2.5 vol%. The withdrawal response of the patient was assigned to one of four stages: 0, no movement; 1, movement at the wrist only; 2, movement below the elbow; 3, movement above the shoulder, general response.

In order to measure the endocrine reaction, blood samples were collected from the antecubital vein of patients on two occasions: at the preoperative visit to the outpatient surgery department and again, immediately after anaesthetic induction for surgery. In these procedures, 2 ml of blood was placed in a serum collection tube for measuring cortisol and 4 ml of blood was put into a tube containing 5.4 mg ethylenediamine tetra-acetic acid to measure ACTH after blood sampling. Glucose was measured as soon as the blood was collected. The serum glucose level was measured using the hexokinase-G6PD method (Denka Seiken, Japan) with a chemistry auto-analyser (TBA-120FR, Toshiba, Japan) as soon as 3 ml of the blood was collected. The tubes were cooled to 4°C in a refrigerator, then the samples were centrifuged (UNION 5KR, Hanil Science Industrial Co. Ltd., Republic of Korea) for 10 min at 3000 ***g***, at 4°C. Serum was collected and stored at −70°C until analysis. Samples from all patients were analysed concurrently, after all of the samples had been collected. In addition, pain scores at 1, 4, 12 and 24 h postsurgery were measured using a visual analogue scale (VAS), where '0' denoted no pain and '10' denoted the most severe pain imaginable. For postoperative pain management, fentanyl 1 mg/kg i.v. was injected at the time of suturing the subcutaneous layer of the surgical site, and one further fentanyl dose was administered (at the same dosage) to patients who had a pain score ≥4 in the recovery room.

Statistical analyses

The SPSS® statistical package, version 12, for Windows (SPSS Inc., Chicago, IL, USA) was used for analyses. Data were presented as mean ± SD or *n* (%) of patients. Demographic data, postoperative pain scores, glucose levels and hormone values were analysed using the Mann–Whitney *U*-test. Withdrawal response for i.v. injection of rocuronium and anxiety score were analysed using the exact X^2-test. A *P*-value <0.05 was considered to be statistically significant.

Results

Fifty patients entered the study; 25 were included in each group. There were no significant differences in age, height or body

weight between the two groups (Table 1). Anxiety scores were reduced significantly in the CES group compared with the control group ($P = 0.016$, Table 2) and withdrawal scores during rocuronium injection were also reduced significantly in the CES group compared with the control group ($P = 0.049$, Table 3). The pain score was significantly lower at 1 and 4 h post surgery in the CES group compared with the control group (Table 4). The number of patients who needed additional analgesia was not significantly different – and ACTH, cortisol and glucose levels were also not significantly different – between the two study groups (Table 5).

Table 1. Demographic data for female patients included in a randomized analysis to study the effects of preoperative cranial electrotherapy stimulation (CES) on perioperative anxiety and stress.

Characteristic	Control group, $n = 25$	CES group, $n = 25$
Age, years	45.8 ± 10.0	49.4 ± 10.3
Weight, kg	65.2 ± 10.8	63.1 ± 9.6
Height, cm	161.7 ± 7.6	159.4 ± 7.2

Data presented as mean ± SD. No statistically significant between-group differences (Mann–Whitney *U*-test).
Control group, no pretreatment; CES group, CES pretreatment.

Table 2. Anxiety scores in patients given cranial electrotherapy stimulation (CES) prior to thyroidectomy compared with those given no pretreatment (control group); $n = 25$ per group.

Anxiety score	Control group, *n* (%)	CES group, *n* (%)
1	3 (12)	8 (32)
2	6 (24)	10 (40)
3	10 (40)	5 (20)
4	6 (24)	2 (8)
5	0 (0)	0 (0)

Anxiety scores graded using a five-point Likert Scale (1, least anxiety; 5, worst anxiety).
Anxiety score, CES group versus control group, $P = 0.016$ (X^2-test).
Control group, no pretreatment; CES group, CES pretreatment.

Discussion

Cranial electrotherapy stimulation is a US Food and Drug Administration-recognized, drug-free treatment for anxiety, depression, insomnia and chronic pain.[11] CES transmits microcurrents in the range between 50 μA and 0.5 mA to the cranium from electrodes attached to the ear lobe.[12] The exact mechanism of action of CES remains unclear; nevertheless, it seems that the microcurrents activate specific neurons in the brainstem and that these neurocytes demonstrate increased ability to produce neurotransmitters such as serotonin, norepinephrine and dopamine.[13] Such neurotransmitters restore the brain's normal biochemical homeostasis after disruption due to stress; they also affect the activity of the nervous system by

Table 3. Incidence and severity of withdrawal responses after rocuronium injection in patients undergoing thyroidectomy given cranial electrotherapy stimulation (CES) or no pretreatment ($n = 25$ per group).

Withdrawal score	Control group, *n* (%)	CES group, *n* (%)
0	8 (32)	11 (44)
1	6 (24)	10 (40)
2	4 (16)	3 (12)
3	7 (28)	1 (4)

Withdrawal response assigned to one of four stages (0, no movement; 1, movement at the wrist only; 2, movement below elbow; 3, movement above shoulder, general response).
Withdrawal response, CES group versus control group, $P = 0.049$ (exact X^2-test).
Control group, no pretreatment; CES group, CES pretreatment.

changing the electrical and chemical activities of brainstem neurons.[13] It is generally thought that CES acts directly on the activities of the limbic system, hypothalamus and reticular activating system of the brain, and has a key role in regulating the activity of brain waves.[14,15] CES induces a relaxed state (known as the alpha state) which reduces stress levels, stabilizes mood and regulates awareness and perception of specific pain types.[9] Therefore, CES may be useful as an adjunct to anxiolytic medication. One 20-min session is often all that is needed to control anxiety effectively for at least a day, and the effects of CES appear to be cumulative.[9]

In this study, the anxiety scores of patients were investigated before they entered the operating room. ACTH, cortisol and blood glucose levels were also compared before and after surgery, in order to perform an objective assessment of anxiety levels due to surgery and anaesthesia. The withdrawal response caused by the pain from injection of rocuronium for anaesthetic induction, and the effects on postoperative pain, were assessed. The study patients were female, and had been diagnosed with thyroid cancer (which one could assume would be accompanied by a high level of preoperative anxiety). The frequency of anxiety was previously found to be increased in cases of urogenital surgery and surgery undertaken due to other malignancies.[16] The preoperative anxiety level was not limited to the time immediately prior to the

Table 4. Postoperative pain scores in patients undergoing thyroidectomy (given cranial electrotherapy stimulation [CES] pretreatment or no pretreatment) measured on a visual analogue scale (VAS).

Group	1 h	4 h	12 h	24 h
Control group, $n = 25$	5.4 ± 1.7	4.1 ± 1.2	2.7 ± 0.9	1.9 ± 0.8
CES group, $n = 25$	3.9 ± 1.0*	3.1 ± 1.0*	2.3 ± 1.4	1.6 ± 0.7

Data presented as mean ± SD.
*$P < 0.05$ compared with control group (Mann–Whitney *U*-test).
Control group, no pretreatment; CES group, CES pretreatment.

Table 5. Serum adrenocorticotropic hormone (ACTH), cortisol and blood glucose levels in patients undergoing thryoidectomy, given cranial electrotherapy stimulation (CES) pretreatment or no pretreatment.

Parameter	Control group, $n = 25$	CES group, $n = 25$
ACTH baseline, pg/ml	47.8 ± 69.5	33.0 ± 18.8
ACTH post induction, pg/ml	44.2 ± 25.3	57.2 ± 53.6
Cortisol baseline, μg/dl	15.2 ± 13.0	11.1 ± 3.2
Cortisol post induction, μg/dl	14.4 ± 5.2	14.1 ± 7.5
Glucose baseline, mg/dl	98.0 ± 9.3	97.1 ± 13.5
Glucose post induction, pg/ml	95.9 ± 11.3	99.4 ± 15.2

Data presented as mean ± SD.
No significant differences between the two groups (Mann–Whitney *U*-test).
Control group, no pretreatment; CES group, CES pretreatment.

procedure but rose from 2 days before, and remained high until 2 days after, surgery.[17] Lichtor et al.[18] reported that anxiety levels experienced in the afternoon of the day before surgery were as high as the levels observed 1 h before surgery. Therefore, in this study, two CES pretreatments were performed: one on the night before and one on the morning of the day of surgery. The present study findings showed that psychological stress before surgery and anaesthesia was significantly decreased in the patients receiving two CES interventions on the day before and on the day of surgery, compared with the control group (which received sham treatment).

The most frequently used anxiolytic method for reducing preoperative anxiety is pharmacological therapy with benzodiazepine-derivative medication, which is likely to be the best method if accompanied with reassurance of the patient through the preoperative visit. In addition to CES, various programmes of psychological therapy have been used. In particular, music therapy, muscle relaxation therapy and humour therapy as adjuvant treatments to reduce preoperative anxiety have been studied.[19–21] Anaesthesiologists already face many clinical options when selecting the most appropriate anaesthetic regimens for patients who require surgery. Faced with such complex decisions, it can therefore be easy to overlook the patient's additional psychological stresses in the lead up to their procedure.

Rocuronium bromide is widely used as a nondepolarizing muscle relaxant and aminosteroid inducer, because of its rapid effects and short duration of action.[22] However, when given via i.v. injection it causes pain in 50–80% of patients.[23] The cause of such pain is unclear, but in general the pain incurred after injecting rocuronium into the peripheral vein is carried through the pleomorphic nociceptors on the venous walls; these nociceptors are influenced by the osmotic pressure (or pH level) of the liquid being injected, so as to cause pain when the osmolarity is $\geq$1.0 Osm/kg, and the pH is $\leq$4 or $\geq$11.[24] When injected after a patient becomes unconscious (following administration of a hypnotic agent), 57–84% of patients showed a withdrawal reflex such as a sudden contraction of the wrist or an arm movement, and the extent of the withdrawal reflex was proportional to the intensity of pain.[25,26] Local anaesthetic, opioid or i.v. anaesthetic agent is injected prior to placing a wider i.v. access, in order to reduce the infusion pain and withdrawal reflexes that are frequently seen in clinical practice.[27] In the present study, CES was associated with a significant decrease in withdrawal response during injection of i.v. rocuronium.

Preoperative stress increases the secretion of ACTH and cortisol via the HPA axis.[5] The stress also affects a wide range of metabolic actions; the degradation of fat and protein is increased, and glucose metabolism is affected.[28] As patients express high levels of preoperative anxiety on the day before and on the actual day of surgery,[17] in the present study, blood samples were taken immediately after induction of anaesthesia as a timepoint to reflect the level of anxiety caused by stress. Somewhat unexpectedly, the measured values of ACTH and cortisol did not show any significant differences between the two groups; elevations in levels of these hormones immediately after induction of anaesthesia would have been expected to be smaller in the CES group compared with those in the control group. Hormonal changes have been observed in patients undergoing surgical procedures that are associated with moderate levels of stress (such as cholecystectomy) or severe stress (such as proctocolectomy), but there were few changes in patients undergoing procedures associated with low levels of stress (such as herniorrhaphy).[7] As mentioned above, the frequency of anxiety is known to be increased in patients undergoing urogenital surgery or surgery for malignancies.[16] In the

case of thyroidectomy, the patient receives much information about thyroid cancer in advance, the surgical site is small with a short operation time, there is a relatively low malignancy level and a good prognosis.[29,30] Consequently, the patient has a relatively low level of stress compared with levels seen before surgery for colorectal, gastrointestinal or breast cancer. Therefore it seems plausible that thyroidectomy does not cause sufficiently large increases in anxiety and stress to impact on ACTH, cortisol and glucose levels. ACTH, cortisol and glucose levels were also not significantly different between the two study groups, in the present study. In a pain study of healthy adult volunteers, the baseline anxiety level before having a pain stimulus was significantly increased compared with the anxiety level in the recovery period from pain, indicating that the increased baseline anxiety was accompanied by elevated levels of ACTH and cortisol, and that patients with high levels of anxiety complained of pain more than patients with low levels of anxiety.[12,14] Kain et al.[4] reported that intramuscular injection of midazolam 30 min before surgery reduced pain for $\leq$7 days postsurgery, which suggests that reduction of preoperative anxiety could result in reduction of postoperative pain.

The study was limited by our failure to consider any possible placebo effects experienced by the control group due to sham treatment. Further research in this area should include three experimental groups: a CES treatment group, a sham group and a placebo controlled group.

In conclusion, CES performed in patients before surgery reduced preoperative anxiety, lowered the level of withdrawal response to rocuronium and reduced postoperative pain scores, but had no effects on the values of ACTH, cortisol or blood glucose. Clinically, when patients exhibit a severe preoperative anxiety state or have risk factors precluding the use of sedatives, anaesthesiologists may be able to use CES pretreatment (with or without pharmacological premedication) on the day before surgery and on the day of surgery itself, to reduce preoperative anxiety and postoperative pain levels.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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