

# Transcutaneous Cranial Electrical Stimulation (Limoge's Currents) Decreases Early Buprenorphine Analgesic Requirements After Abdominal Surgery

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Transcutaneous cranial electrical stimulation with Limoge's currents (TCES) consists of high frequency, low intensity currents which decreased anesthetic requirements during elective surgery. This action is likely to be mediated by the release of central endogenous opioids. In the present study, we hypothesized that TCES applied intraoperatively may decrease early postoperative narcotic requirements. Thirty-nine ASA physical status I and II patients undergoing elective abdominal surgery were enrolled in this prospective, randomized, double-blind, placebo-controlled study. Just before induction of anesthesia, patients were connected to the electrical stimulator and randomly allocated to be either stimulated (TCES group,  $n = 20$ ) or not (control group,  $n = 19$ ) during surgery. The managing anesthesiologist was unaware of which group the patient was assigned. Postoperatively, patients were given a patient-controlled analgesia (PCA) device delivering buprenorphine for the first four postoperative hours.

The recorded variables included postoperative buprenorphine requirements, pain scores (0–10 visual analog scale [VAS]), sedation (0–4 scale), and intraoperative isoflurane requirements. Patients were comparable with respect to age, sex ratio, weight, duration of surgery, intraoperative hemodynamics, fentanyl requirements, and time from skin closure to tracheal extubation. Buprenorphine requirements were significantly reduced in the TCES group versus the control group ( $2.36$  vs  $3.43 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ;  $P = 0.002$ ). Intraoperative isoflurane anesthetic requirements, as well as hourly postoperative scores for pain and sedation, were the same for the two groups. These data indicate that TCES reduces narcotic requirements for early postoperative analgesia. This technique might have potential to facilitate early postoperative analgesia in patients undergoing elective abdominal surgery.

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It has been hypothesized that changes in neuronal plasticity and or nociceptor sensitivity may underly postoperative hyperalgesia (1). Consequently, preventing the functional changes in the central nervous system by preemptive analgesia or other techniques might be beneficial for surgical patients (2). Experiments performed in humans have indicated that low frequency electrical stimulation of the periaqueductal gray matter induces the release of endogenous opioids by depolarization of nerve endings, as assessed by the increased immunoreactivity for  $\beta$ -endorphins in ventricular fluid (3). This results in a rapid and

prolonged pain relief which can be antagonized by naloxone (4).

Several lines of evidence suggest that intraoperative application of transcutaneous cranial electrical stimulation with Limoge's currents (TCES, a particular pattern of electrostimulation consisting of high-frequency, low-intensity alternative currents) may facilitate analgesia in the early postoperative period. TCES enhances the action of opioids in the rat by 30%–40% (5–7). Preliminary results of clinical studies including many surgical patients also appeared promising. TCES increases the analgesic potency of nitrous oxide and reduces opioid requirements during minor surgery by 30%–40% (8,9). These results suggest that TCES applied intraoperatively may facilitate early postoperative analgesia in surgical patients. The aim of the present study was to investigate the effect of intraoperative TCES application on buprenorphine requirements for early postoperative analgesia in patients undergoing elective abdominal surgery.

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**Table 1.** Demographic Patient Data

	TCES (n = 20)	Control (n = 19)
Age (yr)	57.4 ± 3	62.4 ± 2.6
Weight (kg)	75.4 ± 4.8	72.4 ± 4
Sex ratio (F/M)	7/13	8/11

Data are expressed as mean ± SEM; no significant differences were observed.

TCES = transcutaneous cranial electrical stimulation.

## Methods

This study was approved by the Committee of Ethics for Human Research from the Groupe Hospitalier Bichat-Claude Bernard. Thirty-nine ASA physical status I and II patients scheduled for elective abdominal surgery gave written, informed consent to participate in the study. Demographic data are displayed in Table 1. Patients older than 75 yr, with a history of neurologic and/or psychiatric disorder, with chronic obstructive pulmonary disease or scheduled for major surgery with intraoperative blood loss expected to be greater than 2000 mL were excluded from the protocol. Premedication consisted of lorazepam (0.03 mg/kg) given on the evening prior to surgery. Upon arrival in the operating room, a frontal electrode and two posterior electrodes located behind the mastoid bones were placed on the patients' heads. Electrodes were connected to an electric generator via one of four encoded indiscernible cables numbered 1 to 4, only two of which conveyed electric currents. Patients were randomly allocated to be either stimulated (TCES group) or not (control group) from this time until the trachea was extubated. The delay between the connection of patients to the device and the induction of anesthesia never exceeded 15 min.

In the TCES group, the delivered currents consisted of high frequency bursts of bidirectional balanced currents (166 kHz) applied for 4 ms at 100 Hz. In each cycle, the current wave consisted of a nonsquare biphasic sequence where the current was positive for 2  $\mu$ s and negative for 4  $\mu$ s. Because the average intensity was 0 and the frequency of stimulation was high, the possibility of electrode burns due to electrolysis was eliminated. The current intensity averaged 220–250 mA depending on the resistance of the individual patient's head. In the control group, patients were connected to the generator, but not stimulated. Patients were unable to discern actual versus sham TCES.

In the operating room, the usual monitors were used and resultant data recorded every 3 min. Anesthesia was induced with thiopental (6 mg/kg), fentanyl (2  $\mu$ g/kg), and vecuronium (0.1 mg/kg). After tracheal intubation, the circuit was closed and ventilation with 50% N<sub>2</sub>O in oxygen was controlled to

maintain an ETco<sub>2</sub> between 33 and 36 mm Hg. Additional fentanyl (1  $\mu$ g/kg) was administered every 60 min until at least 1 h before skin closure. Isoflurane was administered either when systolic blood pressure was more than –15% of preanesthetic value or when heart rate was more rapid than +15% of that recorded before induction of anesthesia. Additional boluses of vecuronium (0.02 mg/kg) were delivered to maintain the T4:T1 ratio to less than 10%. At the end of surgery, the residual effect of muscle relaxants was antagonized with neostigmine (2.5 mg) and atropine (1 mg) intravenously (IV) and the trachea was extubated. The total dose of fentanyl ( $\mu$ g · kg<sup>-1</sup> · h<sup>-1</sup>) and the isoflurane requirements (mean end-tidal concentration) were calculated for each patient.

Upon arrival in the recovery room, a computerized, patient-controlled analgesia (PCA) device was used to deliver IV buprenorphine (50- $\mu$ g boluses, 30-min lock-out) during the first four postoperative hours and patients were supplemented with nasal oxygen (3 L/min). Metoclopramide was administered when at least one episode of vomiting occurred. The following variables were collected hourly from the first to the sixth postoperative hour by a blinded investigator: rest pain scores, assessed by a visual analog scale (VAS), from 0 = no pain to 10 = worst pain; sedation, from 0 = not arousable to 4 = awake, tense; the buprenorphine requirements ( $\mu$ g · kg<sup>-1</sup> · h<sup>-1</sup>); and the occurrence of undesirable side effects (arterial hemoglobin saturation less than 95%, hypotension, nausea and vomiting).

Data are expressed as mean ± SEM. Quantitative data were compared by the analysis of variance followed by the Student's unpaired *t*-test corrected for the number of comparisons. The  $\chi^2$  test was used for comparison of proportions. A *P* value less than 0.05 was considered the threshold for significance.

## Results

Patients were comparable with respect to age, sex ratio, weight, and duration of surgery (Table 1). In all cases, skin incision consisted of a medial abdominal incision which did not extend superiorly to the xiphoid. Intraoperative hemodynamics (heart rate and systolic blood pressure), fentanyl requirements, and time from skin closure to extubation were comparable between the two groups (Table 2). Similarly, mean end-tidal isoflurane concentrations were nonsignificantly different between the two groups.

Postoperative VAS rest pain scores were not different between the two groups (Figure 1). No episode of arterial desaturation less than 95% SaO<sub>2</sub> was recorded in the two groups during the first six postoperative hours. Also, no episode of vomiting requiring specific antiemetic therapy was recorded. Mild sedation was

**Table 2.** Intraoperative Variables

	TCES (n = 20)	Control (n = 19)
Total fentanyl dose ( $\mu\text{g}/\text{kg}$ )	1.32 $\pm$ 0.07	1.39 $\pm$ 0.1
Duration of surgery (min)	147 $\pm$ 9.6	168 $\pm$ 17.6
Duration of anesthesia (min)	168 $\pm$ 10	192 $\pm$ 18.2
Time from skin closure to extubation (min)	18 $\pm$ 6.1	36 $\pm$ 13.5
Heart rate (bpm)		
Control	81 $\pm$ 2.8	82 $\pm$ 3.2
Tracheal intubation	75 $\pm$ 2.6	76 $\pm$ 2.4
Surgical incision	73 $\pm$ 2.9	71 $\pm$ 2.7
Skin closure	77 $\pm$ 3.2	76 $\pm$ 3.1
Systolic blood pressure (mm Hg)		
Control	148 $\pm$ 5.1	141 $\pm$ 6.2
Tracheal intubation	123 $\pm$ 4.9	113 $\pm$ 4.2
Surgical incision	121 $\pm$ 3.5	120 $\pm$ 5.6
Skin closure	125 $\pm$ 2.7	121 $\pm$ 3.3
Isoflurane (mean end- tidal %)	0.77 $\pm$ 0.08	0.86 $\pm$ 0.11

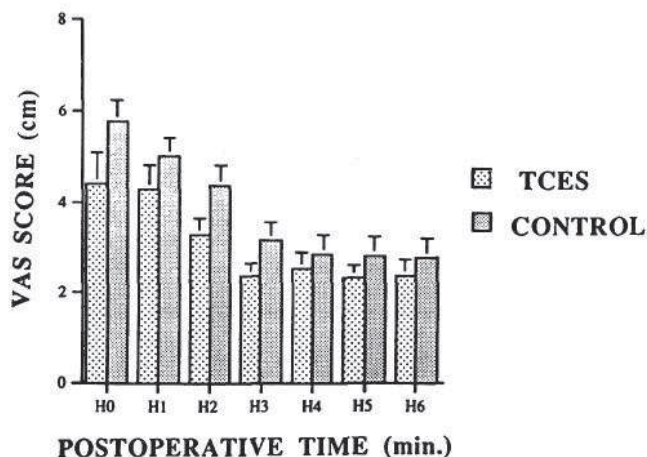
Data are expressed as mean  $\pm$  SEM.  
Fentanyl was administered at a 1- $\mu\text{g}/\text{kg}$  dose every 60 min. The managing anesthesiologist was unaware of which group the patient was assigned to. No significant differences were observed.  
TCES = transcutaneous cranial electrical stimulation.

noted in both groups. There was a highly significant reduction of cumulative buprenorphine requirements in the TCES group compared with the control group (2.36  $\pm$  0.19 vs 3.43  $\pm$  0.29  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ;  $P = 0.002$ ; Table 3). At each postoperative hour, patients required less buprenorphine in the TCES group. However, the difference in buprenorphine consumption achieved statistical significance only at the third and fourth postoperative hours (Table 3). All patients were discharged uneventfully from the recovery room at the sixth postoperative hour.

## Discussion

In the present study, intraoperative application of TCES produced a significant decrease in early postoperative buprenorphine requirements after elective abdominal surgery without causing adverse effects.

Mathematical analysis of Limoge's currents based on the Fourier series indicates that this complex pattern of stimulation allows deep penetration of the electric field into the brain (10). The dielectric properties of biologic tissue convert the high frequency current *in situ* into a combination of a direct and a low frequency current. The latter is thought to depolarize nerve terminals located in medial brain areas and to elicit the release of endorphins and/or enkephalins. This hypothesis is supported by the reduction of halothane minimum alveolar anesthetic concentration in



**Figure 1.** Histograms of the postoperative pain scores measured by a visual analog scale (VAS) in transcutaneous cranial electrical stimulation (TCES) and control groups, from 0 to the sixth postoperative hour (H0-H6).

**Table 3.** Buprenorphine Consumption

Postoperative hours (H)	TCES	Control
H1	1.35 $\pm$ 0.15	1.57 $\pm$ 0.13
H2	0.90 $\pm$ 0.16	1.21 $\pm$ 0.18
H3	0.60 $\pm$ 0.15	1.10 $\pm$ 0.16*
H4	0.60 $\pm$ 0.18	1.00 $\pm$ 0.15*
Total dose ( $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ )	2.36 $\pm$ 0.19	3.43 $\pm$ 0.29†

Data are expressed as mean  $\pm$  SEM.  
TCES = transcutaneous cranial electrical stimulation.  
\*  $P < 0.05$ .  
†  $P < 0.01$ .

rats by TCES, which is reversed by naloxone and potentiated by the enkephalinase inhibitor thiorphan (11). In the experimental studies in which TCES was used in rats, no macroscopic brain damage has been detected (5-7,11). No undesirable side effects attributable to TCES occurred in the clinical studies (8,9).

Although a limited number of patients was included in this randomized, double-blind, placebo-controlled study, they were comparable with respect to demographic characteristics, duration of surgery, intraoperative hemodynamic variations and fentanyl requirements, and time from skin closure to extubation. Also, the duration of connection to the electrical generator was not significantly different in each group. TCES applied under the same experimental conditions decreases the fentanyl dose by 30%-40% during neuroleptanesthesia for minor surgical procedures (9). In the present study, intraoperative application of TCES failed to significantly decrease isoflurane requirements in patients undergoing elective abdominal surgery. However, the data suggest a trend toward lower isoflurane requirements in the TCES

group. In a previous study in which a similar but not identical study design was used, a significant effect of TCES was reported after only 20 min of application, since under these conditions, nitrous oxide potency was increased by 30%–40% in anesthetized patients (8). In contrast, experimental data suggest that a three-hour period of stimulation is necessary to produce a significant (30%–40%) reduction of minimum alveolar anesthetic concentration of halothane in rats (11). The limited number of patients included in this study does not allow us to adequately address the relationship between the duration of stimulation and the decrease in isoflurane requirements. However, it can be speculated that TCES applied three hours preoperatively to surgical patients might have produced a further decrease in isoflurane requirements.

Although buprenorphine has been used successfully for postoperative pain control, it also has some drawbacks when used for IV PCA (12–15). Its association and dissociation constants from opioid receptors are slow, and consequently, its onset of action is rather slow, its duration of effect prolonged, and its action difficult to reverse by naloxone (16). In addition, the number of boluses delivered is expected to be less than that required with a short-acting opioid, which might make it more difficult to demonstrate a significant difference in postoperative narcotic consumption between the two groups. However, we used this drug because it can be administered by a PCA device and is routinely administered postoperatively to patients in our institution. Consequently, only 50- $\mu$ g boluses were allowed, and the duration of the lock-out interval was 30 minutes. Except from mild sedation, no undesirable side effect attributable to buprenorphine was observed in the present study.

The effect of intraoperative TCES on postoperative opioid requirements for analgesia remains to be established. Our findings indicate that TCES applied intraoperatively significantly decreases the early buprenorphine analgesic demand. The VAS pain scores achieved by the patients in the recovery room were similar, and show that buprenorphine was efficient in reducing postoperative pain. The absence of significant differences in the pain scores suggests that the quality of postoperative analgesia was similar in the two groups.

There are several possible explanations for the facilitative effects of TCES on early postoperative analgesia. First of all, experimental data suggest that TCES may act by enhancing the action of narcotics at opioid receptors. Indeed, after a three-hour period of electrical stimulation, TCES enhanced the effect of systemically administered morphine on tail-flick latency in rats (5). However, in the present study, buprenorphine was administered after cessation of TCES application, which makes this hypothesis unlikely. Alternatively,

TCES could stimulate the release of endogenous opioids from enkephalin and/or endorphin-enriched brain structures. Electrical stimulation of the periaqueductal gray matter with low frequency currents produces rapid, long-lasting, naloxone-sensitive analgesia in humans that is associated with increased immunoreactivity for  $\beta$ -endorphins in ventricular fluid (3,4). Moreover, these peptides are involved in long-lasting, naloxone-sensitive analgesia (17–20). Administration of enkephalinase inhibitors also increases analgesia produced by low frequency transcranial stimulation in rats (21). On the other hand, data obtained from clinical trials also support the involvement of endogenous opioids in the analgesic effects of TCES. Stanley et al. (8) observed that N<sub>2</sub>O elicits residual analgesia in surgical patients stimulated intraoperatively, while this was not the case in nonstimulated patients. Also consistent with this hypothesis, we observed that the reduction in postoperative analgesic demand increased with time. Other hypotheses such as the activation by TCES of specific descending pathways resulting in analgesia in the spinal cord, or changes in synaptic plasticity remain to be investigated.

Our results suggest that TCES may have potential to facilitate postoperative analgesia after elective abdominal surgery. However, the place of this technique in routine anesthesia needs further study. Questions to be answered include whether intraoperative TCES facilitates postoperative analgesia during a longer period of time than the first four postoperative hours, whether TCES applied preoperatively affects the requirements for volatile anesthetics as well as the influence of this technique on the time-course of the postoperative recovery of psychomotor brain functions.

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