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Reduced Analgesic Effect of Acupuncture-like TENS but Not Conventional TENS in Opioid-Treated Patients

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Abstract: Evidence from recent animal studies indicates that the analgesic effect of low-frequency transcutaneous electrical nerve stimulation (TENS) is reduced in opioid-tolerant animals. The aim of the present study was to compare the analgesic effect of conventional (high frequency) and acupuncture-like (low frequency) TENS between a group of opioid-treated patients and a group of opioid-naive patients in order to determine if this cross-tolerance effect is also present in humans. Twenty-three chronic pain patients (11 who took opioids and 12 who did not) participated in the study. Participants were assigned in a randomized crossover design to receive alternately conventional and acupuncture-like TENS. There was a significant reduction in pain during and after conventional TENS when compared to baseline for both the opioid and nonopioid group ($P < .01$). For acupuncture-like TENS however, the analgesic effect of TENS was only observed in the nonopioid group ($P < .01$), with opioid-treated patients showing no change in pain scores during and after TENS when compared to baseline ($P > .09$). The reduced analgesic effect of acupuncture-like TENS in opioid-treated patients is coherent with previous animal studies and suggests that conventional TENS should be preferred in patients taking opioids on a regular basis.

***Perspective:** This study shows that patients taking opioids on a regular basis are less susceptible to benefit from acupuncture-like TENS. This phenomenon is probably attributable to the fact that the analgesia induced by acupuncture-like TENS and opioids are mediated by the same receptors (ie, μ opioid receptors).*

***Key words:** Transcutaneous electrical nerve stimulation (TENS), opioids, rehabilitation.*

Transcutaneous electrical nerve stimulation (TENS) is a noninvasive modality commonly used in rehabilitation for pain relief.[30] TENS applications are generally described according to the output characteristics of the device as either high frequency, low intensity (conventional TENS or CT) or low frequency, high intensity (acupuncture-like TENS or AT).[10,14] The high-frequency, low-intensity stimulations employed by CT recruit Aβ fibers which, according to the gate control theory of pain, inhibit the transmission of nociceptive information in the dorsal horn of the spinal cord.[14,27,40] Alternately, the low-frequency, high-intensity stimulations used by AT activate Aδ and C fibers, producing counterirritation analgesia via the recruitment of descending inhibition mechanisms.[43]

There is growing evidence to suggest that the analgesic effect of TENS is associated with the release of endogenous opioids.[8,12,20,38] Interestingly, the type of opioid receptor subserving TENS analgesia would depend on the stimulation parameters used, with high-frequency stimulations producing analgesia through δ opioid receptors and low-frequency stimulations producing analgesia through μ opioid receptors.[20,23,38] The implication of opioid receptors in TENS analgesia could help to explain why the analgesic effect of TENS is sometimes found to decrease after repeated applications.[13] This tolerance phenomenon (which is well documented for opioids)[36] was described by Chandran and Sluka[7] who noticed that animals rendered tolerant to high- and low-frequency TENS were also tolerant to δ and μ opioid agonists, respectively. Moreover, the same group have shown that animals that were made tolerant to morphine (a μ opioid receptor agonist) were also tolerant to low-frequency TENS.[39] In contrast, the analgesic effect of high-frequency TENS (which is believed to act on δ opioid receptors) was preserved in morphine-tolerant rats, suggesting that this cross-tolerance phenomenon is receptor specific.

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If the same results are found in humans, the studies of Sluka et al[7,39] can have several important implications for the clinician. First, they would suggest that AT-tolerant patients would retain less benefits from opioid analgesics than patients who are not tolerant to AT. Second, they would propose that the analgesic effect of AT would be considerably decreased in opioid-tolerant patients. In 1980, Solomon et al[41] reported that the analgesic effect of TENS for postoperative pain was reduced in patients who had used narcotics prior to surgery compared to patients who had not used narcotics before surgery. These results suggests that the cross-tolerance phenomenon observed between TENS and opioids in rodents is also present in humans.[39] Nevertheless, 2 important limitations prevent us from making clear assertions. First, the results of Solomon et al were based on posteriori analyses and should therefore be considered exploratory until confirmed by other studies. Second, and most importantly, the stimulation parameters for TENS were not specified by Solomon et al, making it impossible to determine if the cross-tolerance effect observed by the authors were between opioid analgesics and AT or between opioid analgesics and CT. Thus, the purpose of this study was to compare the analgesic efficacy of CT and AT between a group of patients who took opioids on a regular basis and a group of patients who did not use opioids for more than 6 months. Based on the work of Sluka et al,[39] we hypothesized that the analgesic efficacy of AT (but not CT) would be decreased in patients who took opioids on a regular basis.

Methods

Participants

Twenty-three chronic pain patients (11 who took opioids on a daily basis for more than 4 months and 12 who did not use opioids for more than 6 months) participated in the study. Four patients from the nonopioid group previously took opioids for their pain condition but the medication was stopped more than 6 months before testing (mean time since medication was stopped $\pm$ SD = 25.8 $\pm$ 23.9 months). Participants were recruited through ads posted in local newspapers, physiotherapy clinics and in the Sherbrooke University Hospital's Pain Clinic. All participants had localized pain of diverse origin (eg, spinal disc herniation, osteoarthritis, chondromalacia) for more than 6 months. For security reasons, patients with demand-type cardiac pacemakers and pregnant women were excluded. Every participant was asked to refrain from using short-term analgesics 2 hours before testing and from taking caffeine and smoking cigarettes 6 hours before testing. Participants' characteristics are presented in Tables 1 and 2.

The experiment took place at the Clinical Research Centre of the Sherbrooke University Hospital, in Sherbrooke, Quebec, Canada. The Research Ethics Board for Human Subjects of the Sherbrooke University Hospital approved the study's procedures and each participant provided informed consent before participation.

Experimental Design and TENS Stimulation Protocol

Participants were assigned in a randomized crossover design to receive, alternately, CT and AT. The order of presentation of the 2 types of TENS stimulations was determined using a random number table. This resulted in 11 participants receiving CT before AT, and 12 participants receiving AT before CT. Every participant was submitted to the 2 types of stimulation (approximately 1-week interval). At each visit, a thorough examination was made by the experimenter to determine the precise location of the pain. The painful area's margins were marked carefully with a pen in order to ensure optimal electrode placement. Participants were placed in a comfortable position, generally lying on their stomach (ventral decubitus) on a mobilization table. Pillows were given to ensure proper positioning.

TENS stimulations were delivered using a pair of rubber silicone electrodes connected to a digital Eclipse Plus apparatus (Empi, St Paul, Minnesota). The electrodes were placed over the painful area identified previously. Electrodes' position was reassessed with the TENS stimulator turned ON in order to be certain that the induced paresthesias entirely covered the painful region. In cases where stimulations did not properly cover the painful region, the stimulator was turned OFF and the electrodes were repositioned. For CT, the frequency was set at 100 Hz, the pulse duration at 60 μs, and the intensity was adjusted to produce strong and comfortable (innocuous) tingling sensations. For the AT, the frequency was set at 3 Hz, the pulse duration at 250 μs, and the intensity was adjusted to produce strong and painful sensations (pain tolerance threshold). For both CT and AT, the stimulation was applied for 25 minutes and the intensity was occasionally raised (based on the participant's sensation) to account for nerve accommodation and to maintain the same level of sensation.[34,42]

Pain intensity and unpleasantness was evaluated using 2 separate numerical rating scales (NRS) (intensity 0 = no pain, 100 = most intense pain imaginable; unpleasantness 0 = not unpleasant, 100 = most unpleasant pain imaginable). Pain intensity (sensory-discriminative component) and unpleasantness (motivational-affective component) are 2 distinct components of pain which are associated with distinct anatomical regions of the pain matrix.[2] The distinctions between pain intensity and pain unpleasantness was explained successfully to the participants by using the analogy of Price et al.[32] Participants were asked to evaluate the intensity and unpleasantness of their clinical pain at 3 occasions: 1) before TENS application; 2) during TENS application (ie, after 15 minutes of stimulation); and 3) immediately after TENS application. The Patient Global Impression of Change (PGIC) scale was also used after each TENS application to document participants' overall evaluation of their treatment.[11,18]