ANALGESIC AND ANTIHYPERALGESIC EFFECTS OF TRANSCRANIAL ELECTROSTIMULATION WITH COMBINED DIRECT AND ALTERNATING CURRENT IN HEALTHY VOLUNTEERS

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Background: Transcranial electrostimulation (TES) is a non-invasive, neuromodulating brain stimulation technique, where an electrical current is administered through the electrodes positioned on the skin of the subject's head. Diverse TES modalities have been suggested (e.g. transcranial direct current [DC] stimulation, different types of alternating current [AC] stimulation, etc.), and some of them have been reported to produce clinically-significant analgesia. However, lack of randomized, double blind TES human studies, the observed insidious onset of TES-induced analgesia, and either absent, or questionable concomitant reduction in patients' pain medication requirements, leave an issue of a true antialgesic potency of TES open to speculation.

The purpose of this study was to investigate whether the use of TES with combined DC and 60 Hz AC current (TES_{60Hz}) (Figures 1-2), is capable of producing hypoalgesic and antihyperalgesic effects in human subjects, in response to experimentally-induced heat and mechanical pain in normal and inflamed skin. Our previous rat studies have demonstrated that TES_{60Hz} exerts significant, modality-specific antinociceptive effect, while TES_{100Hz} can serve as a suitable active control. In this study, antihyperalgesic effects of TES were investigated in a validated experimental model of inflammatory pain produced by ultraviolet B skin irradiation (UVB, or sunburn lesion). The UVB lesion features many components of an acute inflammatory response associated with surgery, tissue injury and inflammatory diseases (e.g. arthritis), including sensitization of peripheral nociceptors and induction of a primary hyperalgesic state. It also demonstrates high sensitivity to antihyperalgesic effects of anti-inflammatory drugs and opioids, making it possible to compare the magnitude of TES-induced behavioral effects with those of benchmark pharmacological treatments.

Methods: Quantitative sensory testing (QST) (Figure 3) evaluating heat and mechanical pain thresholds in normal skin and UVB lesion, was performed in 20 healthy male subjects during 35 min TES session, and 45 min after TES was discontinued. The study was conducted in a double-blind, randomized, two way crossover fashion, with a 7 day wash-out period. Treatment effects were analyzed with a linear mixed-effects modeling approach, using the lme function of S-Plus. $P<0.05$ was considered statistically significant.

Results: TES evoked significant, rapidly developing, frequency dependent ($TES_{60Hz} > TES_{100Hz}$), thermal and mechanical antihyperalgesic effects in the UVB lesion, and attenuated thermal pain in unimpaired skin (Figures 4-5). No long-lasting analgesic and antihyperalgesic effects of a single TES treatment were demonstrated in this study.

Discussion: TES_{60Hz} significantly reduced primary thermal and mechanical hyperalgesia in the UVB lesion, revealing its ability to modulate the activity of primary nociceptors (C and A delta fibers). Indirect QST comparison places Remifentanil as 2-2.5 times more effective than TES_{60Hz} in attenuating thermal pain and hyperalgesia (Figure 4); however, the estimated steady state blood concentrations producing these effects would correlate with those required to reduce the minimum alveolar concentration (MAC) of isoflurane by 50%, and block the sympathetic responses to skin incision in 50% of patients (EC_{50}) receiving target controlled propofol anesthetic, respectively.

The effect of TES_{60Hz} on thermal pain was predominantly hyperalgesic (Figure 4). This contrasts strongly with the similar thermal analgesic and antihyperalgesic activity observed for opioids, suggesting that the mechanism of TES action may not be directly related to the release of endogenous opioids, as has been thought previously. This speculation is further supported by the capacity of TES_{60Hz} to significantly attenuate primary mechanical hyperalgesia in the UVB lesion (Figure 5). Primary mechanical hyperalgesia is thought to be mediated by activation of silent, high threshold mechano-insensitive A delta and C afferents, and particularly silent C nociceptors, which are not as potently affected by opioids as C-nociceptors responsible for thermal pain and hyperalgesia (Figure 5). Furthermore, the fact that silent C-nociceptors are strongly implicated in the development of central sensitization highlights possible beneficial role of TES in reducing central hyperexcitability.

Conclusions: The TES-induced analgesia appears to be clinically relevant. A seeming ability of TES to effectively modulate both peripheral sensitization of nociceptors and altered central processing of the nociceptive input, presumably by non-opioidergic mechanism(s), suggests the potential role of TES in clinical pain management. The future of this technique will rest on the confirmation studies exploring TES effects in experimental human pain models of secondary hyperalgesia and allodynia, and demonstrating presence of the analgesic and antihyperalgesic aftereffects after prolonged or repetitive TES application.

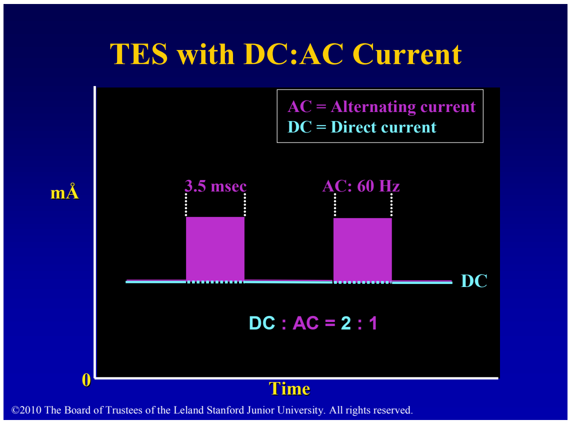

Figure 1: Transcranial electrostimulation (TES) with combined direct (DC) and alternating (AC) current: TES current characteristics.

TES current is represented by a combination of DC offset and "superimposed" AC pulse trains (pulse duration 3.5 msec). The optimal AC frequency for producing antinociceptive and analgesic effects is 60 Hz (TES_{60Hz}). The ratio of DC to AC intensity is 2:1 (in this study, the intensity of current was 5 mA, meaning that the DC intensity was approximately 3.4 mA, and AC intensity 1.7 mA).

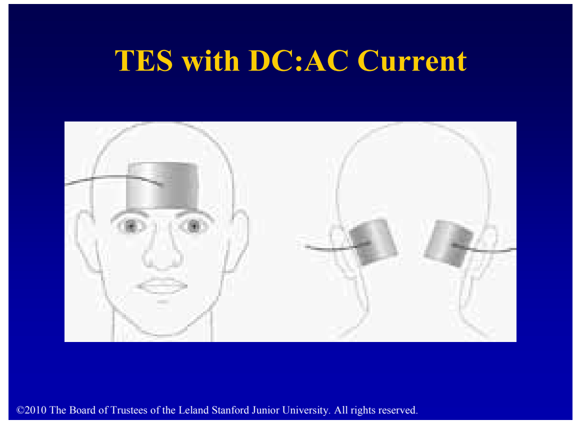

Figure 2. Transcranial electrostimulation (TES) with combined direct and alternating current: TES electrode positioning.

TES is administered through a single frontal cathode and paired anodes, positioned behind the mastoid processes. The electrodes are held in place by Velcro straps.

Figure 3: Transcranial electrostimulation (TES) with combined direct and alternating current: Quantitative Sensory Pain Testing (QST).

During TES, heat pain thresholds (HPT, left) were tested with a hand-held thermode (16 x 16 mm) of the thermal sensory analyzer (TSA 2001, Medoc Advanced Medical Systems, Minneapolis, MN), by ramping up the skin heating temperature to 52°C (cut-off). The feedback loop, triggering the recording of HPT and cooling of the thermode, was activated by the subject pressing on the computer mouse. Mechanical pain thresholds (MPT, right) to impact stimuli were tested with the weight calibrated punctuated pressure probes, applied to the subject's skin in random alternating ascending and descending sequence, to elicit "yes-no" MPT responses.

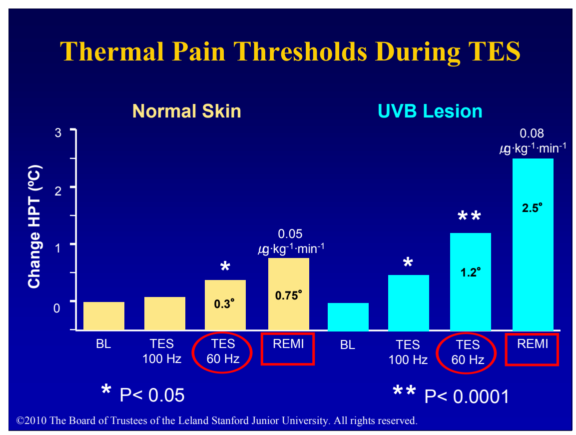

Figure 4: Transcranial electrostimulation (TES) with combined direct and alternating current: thermal analgesic and antihyperalgesic effects, and their comparison with the effects of intravenous opioids (Remifentanil).

HPT – heat pain threshold; BL – baseline (pre-TES); Remi – remifentanil.

Compared to the effects of remifentanil elicited in similar experimental pain models and pain testing paradigms, TES60Hz appears to be 2.5 times less potent than remifentanil (0.05 mcg·kg-1·min-1, estimated steady state blood concentration 1.3 ng·ml-1) in alleviating thermal pain in unimpaired skin, and twice less potent than remifentanil (0.08 mcg·kg-1·min-1, estimated steady state blood concentration 2 ng·ml-1) in attenuating primary thermal hyperalgesia in UVB lesion.

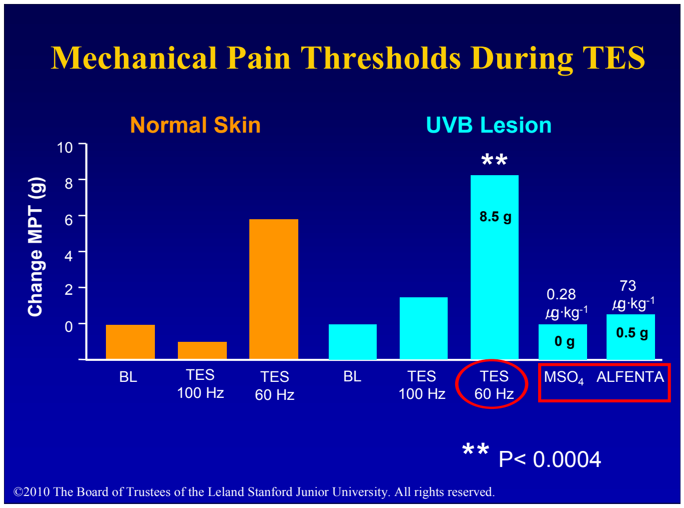

Figure 5: Transcranial electrostimulation (TES) with combined direct and alternating current: mechanical antihyperalgesic effect, and its comparison with the effects of intravenous opioids.

MPT – mechanical pain threshold; BL – baseline (pre-TES); MSO_4 – intravenous (IV) morphine; Alfenta – intravenous (IV) alfentanyl.

A significant mechanical antihyperalgesic effect of TES_{60Hz}, compared to absent/minimal effect of large doses of IV morphine and alfentanyl in primary hyperalgesic thermal skin burn lesion. There was a also a strong trend for TES_{60Hz} to attenuate mechanical pain in normal skin (P=0.09), suggesting that a larger study sample might have detected the modulating effect of TES_{60Hz} on A delta fibers, responsible for phasic mechanical pain transmission.

REFERENCES:

- Nekhendzy V, Fender CP, Davies MF, Lemmens HJ, Kim MS, Bouley DM, Maze M. The antinociceptive effect of transcranial electrostimulation with combined direct and alternating current in freely moving rats. Anesth Analg 2004;98(3): 730-7
- Gustorrf B, Hoechtl K, Sycha T, Felouzis E, Lehr S, Kress HG. The effects of remifentanil and gabapentin on hyperalgesia in a new extended inflammatory skin pain model in healthy volunteers. Anesth Analg 2003;98:401-7
- Gustorrf B, Felleiter P, Nahlik G, Brannath W, Hoerauf KH, Spacek A, Kress HG. The effect of remifentanil on the heat pain threshold in volunteers. Anesth Analg 2001;92:369-74
- Koppert W, Likar R, Geisslinger G, Zeck S, Schmelz M, Sittl R. Peripheral antihyperalgesic effect of morphine to heat, but not mechanical, stimulation in healthy volunteers after ultraviolet-B irradiation. Anesth Analg 1999;88:117-22
- Lotsch J, Angst MS. The mu-opioid agonist remifentanil attenuates hyperalgesia evoked by blunt and punctuated stimuli with different potency: a pharmacological evaluation of the freeze lesion in humans. Pain 2003;102:151–61
- Schmelz M. Translating nociceptive processing into human pain models. Exp Brain Res 2009;196:173–8
- Lang E, Kapila A, Shlugman D, Hoke JF, Sebel PS, Glass PS. Reduction of isoflurane minimal alveolar concentration by remifentanil. Anesthesiology 1996;85:721-8
- Albertin A, Casati A, Federica L, Roberto V, Travaglini V, Bergonzi P, Torri G. The effect-site concentration of remifentanil blunting cardiovascular responses to tracheal intubation and skin incision during bispectral index-guided propofol anesthesia. Anesth Analg 2005;101:125-30
- Munoz HR, Cortinez LI, Ibacache ME, Altermatt FR. Remifentanil requirements during during propofol administration to block the somatic responses to skin incision in children and adults. Anesth Analg 2007;104:77-80
- Schmelz M, Schmidt R, Ringkamp M, Handwerker HO, Torebjoerk HE. Sensitization of insensitive branches of C nociceptors in human skin. J Physiol 1994;480:389-94
- Schulte H, Solevi A, Segerdahl M. Dose-dependent effects of morphine on experimentally induced cutaneous pain in healthy volunteers. Pain 2005; 116:366–74