Original Article

Electrocortical Analysis of Patients with Intercostobrachial Pain Treated with TENS after Breast Cancer Surgery

Julio Guilherme Silva, PhD, PT[1, 2]*, Camila Gonçalves Santana[2],
Kelly Rosane Inocêncio[3], Marco Orsini[1], Sergio Machado[4, 5], Anke Bergmann[2, 6]

[1] *Department of Physical Therapy, Federal University of Rio de Janeiro (UFRJ), Brazil*
[2] *Rehabilitation Science Masters Program, Augusto Motta University Center (UNISUAM): Praça das Nações, n° 34 − 3° andar. Bonsucesso, Rio de Janeiro, CEP 21.041-021, Brazil*
[3] *Municipal Rehabilitation Center (CMR), Department of Physical Therapy in Oncology, Brazil*
[4] *Panic and Respiration Laboratory, Institute of Psychiatry, Federal University of Rio de Janeiro (UFRJ), Brazil*
[5] *Quiropraxia Program, Central University, Chile*
[6] *National Cancer Institute (INCA), Brazil*

Abstract. [Purpose] Among the physical therapeutic procedures to decrease pain, there is transcutaneous electrical neural stimulation (TENS). There is no consensus about its efficacy for oncological patients, especially for postmastectomy pain and eletrocortical changes in somatosensory areas. The aim of this study was to analyze acute electrocortical changes after TENS treatment of patients with intercostobrachial post mastectomy pain. [Subjects] Eighteen patients were divided into acupuncture (A) and burst (B) group. [Methods] In this pre and post-intervention study each group was measured for EEG analysis in absulte power in alpha band (8–14 Hz). Outcomes variables were the alpha waveband in the sensorymotor cortex and pain pre-and-post TENS intervention. Data were analyzed using ANOVA to compare times (rest, 10 and 15 min), group and electrodes. Pain was analyzed using percentual pain evaluation (PPE) in both groups. [Results] Outcomes indicate main effects of time and electrodes because of slow (8–10 Hz) and fast alpha (10–12 Hz) wavebands decreased. PPE reduced 88.4% in A and 66.3% in G. [Conclusion] TENS promoted electrical modification in the parietal region and a decrease in pain. Future studies should investigate other wave must be proposed for other bands and use different methods of EEG analysis to elucidate the actual mechanisms behind the efficacy of TENS treatment.
Key words: Transcutaneous electric nerve stimulation, Mastectomy, Electroencephalography

(This article was submitted Aug. 13, 2013, and was accepted Sep. 22, 2013)

INTRODUCTION

Breast cancer is the second most frequent type of cancer worldwide, and is the most common cancer among women[1]. The National Cancer Institute of Brazil, (INCA) registered around 50 thousand cases of breast cancer in 2012, with an estimated risk of 49 cases per 100 thousand women[2]. The routine procedure for staging and management of breast cancer is the axillary lymph node dissection or lymph node biopsy. These procedures cause anatomical injury which may result in lymphedema[3], nerve injury, shoulder dysfunction or pain[4].

Post-mastectomy pain syndrome is a pain that persists over a 3-month period. It is defined as a chronic pain that begins after breast cancer surgery. It is frequently located in the anterior or lateral regions of thorax, axillary and/or medial upper arm, and is experienced as burning pain, shooting pain, pressure sensation or numbness[4]. Jung et al.[5] distinguished four subtypes of neuropathic pain resulting from breast cancer surgical treatment: phantom breast syndrome, neuralgia, intercostobrachial nerve pain, neuroma and pain of other nerve injuries.

In Brazilian studies, the incidence of pain syndrome 6 months after breast cancer surgery is 52.9% and it is associated with younger age (<40 years) and axillary lymphedenectomy when more than 15 lymph nodes are removed. The incidence of intercostobrachial pain is 52.9%, that of shoulder pain is 27.2%, phantom breast pain in 3.2% and that of neuroma is 1.3%[4]. The management of pain syndrome is complex and multidimensional with several forms of intervention. There is a growing interest in investigating alternative therapeutic approaches, such as transcutaneous nerve electrical stimulation (TENS)[7, 8], in oncology. TENS is a non-invasive technique used to promote the symptomatic relief of acute and chronic pain, its mechanism of ac-

*Corresponding author. Julio Guilherme Silva (E-mail: jgl-silva@yahoo.com.br)

tion is based on the gate theory of pain[8]. In oncology and palliative setting, TENS has been used to control acute and chronic pain, partly because of its low cost, favorable side-effect profile and safety[9]. Nevertheless, investigations of the therapeutic effects of TENS on brain activity have been rare scarce, especially, in women with intercostobrachial nerve pain due to breast cancer treatment. Both TENS (acupuncture and burst) have effects on the neurophysiological activities of receptors and also induce the expression of endogenous opioids[6]. Because of this, there is a need to investigate the electrical cortical behavior during TENS interventions.

Within this context, this study aimed to verify the acute effects of the electrical activity in the somatosensory cortex of two different types of TENS, i.e. acupuncture and burst, as a therapy for breast cancer patients with intercostobrachial nerve pain. Since it is known that the main areas involved in pain mechanisms are the somatosensory areas (i.e., parietal areas), we hypothesized that different patterns of parietal EEG activity would be induced by administration of TENS acupuncture and burst.

SUBJECTS AND METHODS

A randomized clinical trial study was conducted of breast cancer patients who had pain syndrome due to intercostobrachial nerve injury. Eighteen patients were recruited by the physical therapy service. Inclusion criteria were: absence of mental impairment determined by a score of ≥ 27 in the Mini Mental State Examination (MMSE); no history of psychoactive or psychotropic substance use (screened by a previous anamnesis and a clinical examination); and intercostobrachial nerve pain present ipsilateral the operated side. The exclusion criteria: any other local or systemic pain condition; less than 6 to 8 hours of sleep prior to the experiment; and intake of caffeine 48 hours prior to the experiment.

All subjects were informed the experimental protocol and signed a consent form before participating in this study. The study was approved by the Ethics Committee of Augusto Motta University Center (number 019/2011), in compliance with the rules provided for research on human subjects contained in the Resolution of the National Health Council.

Eligible participants were randomly distributed to Group A − TENS Acupuncture (n = 9) or Group B − TENS Burst (n = 9). At the time of TENS application, the patients were blind regarding the treatment group they were in, as well as the procedure to be performed. EEG of subjects in both groups was measured, at rest and 10 and 15 min after TENS application. EEG was recorded simultaneously the TENS application. The EEG analysis was carried out at home and on the tenth minute during the application of TENS. We used a two-channel microcomputer-controlled electro-stimulator (Ibramed − Neurodyn Portable TENS/FES, Brazil). Among the possible modalities of TENS, we chose TENS acupuncture and burst. Our choice was based on thier similarity in the application times needed to obtain analgesia (10–15 min). TENS acupuncture is pre-programmed with

an automatic range of intensity and frequency, with a descending pulse time of 275 μs and a rising pulse of 175 μs and increasing pulse repetition frequency from 5 to 25 Hz over a period of 12.5 s. TENS burst is also programmed with 7 pulses of cycle on of 28 ms and cycle-off of 472 ms (2 Hz) with a pulse time of 150 μs.

The International 10/20 System[10] for electrodes was used with 20-channel EEG system (BrainNet BNT-EEG EMSA-Medical Instruments, Brazil). The 20 electrodes were arranged in a nylon cap (ElectroCap Inc., Fairfax, VA, USA) to record monopolar derivations from reference electrodes attached to the earlobes. In addition, two 9-mm diameter electrodes were attached above and on the external corner of the right eye, in a bipolar electrode montage, for monitoring eye-movement (EOG) artifacts. The impedance of EEG and EOG electrodes was kept between 5–10 KΩ. The data acquired had total amplitude of less than 100 μV. The EEG signal was amplified with a gain of 22,000, analogically filtered between 0.01 Hz (high-pass) and 100 Hz (low pass), and sampled at 240 Hz. The software EEG-Captação (EMSA-DELPHI 5.0) was used for EEG acquisition.

First, EEG signals were evaluated by visual inspection. We then we used independent component analysis (ICA) to identify the sources of artifacts (i.e., blink, muscle and saccade-related artifacts). Next, we removed those portions of the EEG record that clearly showed blink-related artifacts "influence" by visual inspection and those that showed blink-related artifacts "contamination" according to ICA. The data were collected using the bi-auricular reference electrodes and they were transformed (re-referenced) using the average reference after we conducted the artifact elimination using ICA. The power spectral density (PSD) was calculated directly from the square modulus of the FFT (Fast Fourier Transform). The calculation was performed using MATLAB 5.3 (Mathworks, Inc.). We extracted quantitative EEG parameters within a time window of 4s before and after the treatment. Thereafter, all raw EEG trials were visually controlled and trials contaminated with ocular or muscle artifacts were discarded. The FFT resolution was 1/4 s–0.25 Hz. To examine a stationary process, the "Run-test" and "Reverse-Arrangement test" were applied. Specifically, the stationary process was accepted for each 4s period (epoch's duration). In this way, the threshold was defined as the average plus three standard deviations in artifact-free EEG; periods showing a total power higher than this threshold were excluded from the analysis.

Therapeutic outcome was assessed using the Visual Analogical Scale (VAS) with a score of 0 indicating "no pain" and a score of 10 indicating "intolerable pain". The subjects self-assessed initial pain (IP) and final pain (FP) after TENS intervention. After this, the changes of pain was calculated due percent pain evaluation (PPE) with the formula PPE = [(IP − FP)÷ IP] × 100%.

The parietal lobe was chosen because of its involvement in sensory processes, such as pain[10, 11]. Thus, we selected the electrodes P3, Pz and P4 for absolute power analysis and we divided alpha band in slow (8–10 Hz) and fast alpha (10–12 Hz). Absolute power was defined as the total energy intensity of an electrode on a certain region in the differ-

Table 1. Group A (Acupunture)

Subject	Age	Type of surgery	VAS (Pre)	VAS (Post)	% Pain reduced	Duration of surgery (months)
1	69	Mastectomy	2	0	100	12
2	43	Mastectomy	3	0	100	24
3	61	Segmentectomy	2	0	100	12
4	61	Mastectomy	7	1	85.8	8
5	57	Mastectomy	7	1	85.8	25
6	61	Mastectomy	4	1	85.8	21
7	43	Mastectomy	7	1	85.8	24
8	48	Mastectomy	7	1	85.8	18
9	57	Mastectomy	6	2	66.7	13
Mean (SD)	55.9 ± 8.99				88.4 ± 10.7	17.4 ± 6.37

VAS: Visual analogical Scale, Pre and Post (after 15 min) TENS intervention, % Percent pain reduced; SD: Standard Deviation

Table 2. Group B (Burst)

Subject	Age	Type of surgery	VAS (Pre)	VAS (Post)	% Pain reduced	Duration of surgery (months)
1	57	Mastectomy	8	2	75	12
2	50	Mastectomy	2	0	100	3
3	51	Mastectomy	5	0	100	13
4	48	Mastectomy	10	7	30	15
5	68	Mastectomy	7	3	40	36
6	61	Mastectomy	10	5	50	9
7	53	Segmentectomy	9	4	55.6	27
8	47	Mastectomy	8	2	75	20
9	44	Mastectomy	7	2	71.5	21
Mean (SD)	53.2 ± 7.58		7 (mode)	2 (mode)	66.3 ± 24.6	17.3 ± 9.9

VAS: Visual Analogical Scale, Pre and Post (after 15 min) TENS intervention; (%) Percent pain evaluation; SD: Standard Deviation

ent frequency bands[12]. For the sample size calculation, we considered women with intercostobrachialgia nerve pain receiving physical therapy. We estimated an improvement of 30% in pain, with a confidence interval (CI) of 95% and with a power of 80%. Therefore, 9 patients were required in each group, for a total of 18 subjects.

Subjects' characteristics and sociodemographic data are presented using descriptive statistics (i.e., mean and SD). Pain was analyzed due modal value and the comparison of PPE (i.e. pre and post TENS intervention) in both groups. With respect to EEG data, absolute alpha power was the dependent variable of interest. The statistical analysis of absolute alpha power was performed using the software SPSS version 17. Data were transformed in Log_{10} for approximation to normal distribution[13]. The Kolmogorov-Smirnov test was used to test the distribution of the EEG data. When the data showed a normal distribution, was used ANOVA to compare pre- and post-treatment values of (i resting EEG and 10 and 15 min of each group with a significance level of 95% ($p \leq 0.05$). The analysis was limited to three three topographically representative electrode of the parietal cor-

tex: P3, Pz and P4).

RESULTS

Eighteen patients with a mean age of 54.38 years old (SD 8.153) were studied. Tables 1 and 2 show the general characteristics of the subjects (mean ± SD), as well as the results of VAS (pre and post-intervention) and PPE and type of surgery for each of the two groups (TENS acupunture and burst).

After the EEG analysis showed there were a decreases in slow and fast alpha absolute power in both groups, in all electrodes. In the acupuncture group, compared to at rest the slow alpha average at rest decreased by more than half 15 min at all electrode: Pz (0.178 to 0.078 μV^2 Log_{10}); P3 (0.189 to 0.096 μV); P4 (0.199 to 0.079 μV), and all the differences were significant: p=0.009; p=0.005; p=0.002, respectively (Table 3).

As for the fast alpha, there was a slight decrease at the P4 electrode from 0.207 μV at rest to 0.197 μV at (Table 3). However, the energy pattern remained similar to the slow

Table 3. Acupunture group: slow and fast alpha

Electrode	Slow Alpha				Fast Alpha			
	Resting EEG (μV^2 Log$_{10}$)	EEG 10 min (μV^2 Log$_{10}$)	EEG 15 min (μV^2 Log$_{10}$)	p	Resting EEG (μV^2 Log$_{10}$)	EEG 10 min (μV^2 Log$_{10}$)	EEG 15 min (μV^2 Log$_{10}$)	p
PZ	0.178	0.107	0.078	*	0.192	0.119	0.073	*
P3	0.189	0.132	0.096	*	0.177	0.158	0.101	*
P4	0.199	0.121	0.076	*	0.207	0.197	0.082	*

* statistical significance (p<0.05)

Table 4. Burst group: slow and fast alpha

Electrode	Slow Alpha				Fast Alpha			
	Resting EEG (μV^2 Log$_{10}$)	EEG 10 min (μV^2 Log$_{10}$)	EEG 15 min (μV^2 Log$_{10}$)	p	Resting EEG (μV^2 Log$_{10}$)	EEG 10 min (μV^2 Log$_{10}$)	EEG 15 min (μV^2 Log$_{10}$)	p
PZ	0.208	0.120	0.076	*	0.201	0.134	0.091	*
P3	0.189	0.154	0.082	*	0.173	0.162	0.112	*
P4	0.177	0.131	0.098	*	0.204	0.174	0.089	*

* statistical significance (p<0.05)

alpha at the P3 and Pz electrodes. P3 and PZ showed progressive decreases in absolute power

The results for group B were similiar. There were decreases in absolute slow alpha power at all electrodes (P3, Pz and P4) all of which were significant p=0.01; p=0.04 and p=0.008 respectively. The changes between rest and 10 min were greater than the change between 10 and 15 min (Table 4).

In fast alpha band, in the burst group, there was also a decrease in absolute alpha power more intense in Pz (0.201 µV to 0.091 µV) and P4 (0.204 to 0.089 µV) electrodes between the rest and 15 min moment conditions. But in P3 the fall was less accentuated. In all electrodes P3, P4 e Pz, the differences were significant with main effect fot the moment (p=0.03; p=0.005 e 0.012) respectively (Table 4).

DISCUSSION

Our study aimed to investigate the acute effects of TENS acupuncture and burst on the parietal EEG activity of breast cancer patients with intercostobrachial nerve pain. Our results show there were decreases in pain sensation in both groups. In the burst group, the difference between pre- and post-treatment was 4 points in VAS and 66.3% pain reduced in PPE. The pain difference in the acupuncture group was also 4 points and an 88.4% reduction for PPE. These results provide further evidence that TENS application for patients with breast cancer relieves pain due to the analgesic effect. The physiological mechanism of TENS action is postulated to be electrical stimulation through the skin inhibiting the transmission of pain impulses through the spinal cord, as well as the release of endogenous opioids, as endorphins, by the brain or the spinal cord[14–16].

The complexity of the neurophysiological mechanisms suggests the need for multiple methods to appropriate control. The most commonly used drug substances for the control of postoperative pain are the opiates, which are inhibitors of type C-fibers. Approximately 75% of spinal opioid receptors are found surrounding the presynaptic C-fiber. However nerve fibers of A-Delta type are not inhibited by the drug, therefore, the use of other techniques is needed in order exercise adequate pain control. TENS reduces nociceptive activity evoked in cells of the medullary dorsal horn when applied in receptor areas. It activaes myelinated nerve fibers afferent of lager diameter the smaller diameter C fibers, which are not myelinated and have slower conduction and are unable to transmit a nerve impulse[14, 17, 18].

Results of this study corroborate the evidence of a study in which volunteers were instructed not to use the drug, indicating that the pharmacological extra feature proved to be successful for pain inhibition, justifying the activation of A-delta and C- fibers for the results that were found.

Another mechanism for analgesia, as mentioned above, is the release of opioids, through what we call the pain suppression system. This activation increases the synthesis of neurotransmitters such as endorphins, enkephalins, serotonin, among others (endogenous opioid system and serotonin), which inhibit activity over the components of the nociceptive system, by modulation of the neuronal transmission activity located in the medullary dorsal horn[15, 19, 20]. Both types of current (acupuncture and burst) used in this study reduced of pain, which is reflected in explains the similar VAS's results.

The results show a decrease in slow and fast absolute alpha power during TENS application compared to the resting state, reflecting greater activation of the parietal region. This region is known to be responsible for orientation and attention toward painful sensory stimuli, and is described in literature describing it as a multimodal association area[21]. We verified a decrease slow and fast alpha rhythms in parietal cortex during TENS application. Studies have indicated that slow alpha is associated to non-specific brain

processes to the type of task (energy demands), while fast alpha is related with specific somatosensory processes[22, 23]. A decrease in alpha activity is associated with a state of high excitability and low inhibitory control, while an increase in alpha activity represents a low excitability and is related to a relaxed condition. Thus, our results can be interpreted as greater attention to the painful processes during the TENS application.

This suggests that during the experiment the subjects were aware of the painful processes. This finding is consistent with the literature and indicates that changes in the alpha band related to pain[21].

In addition, the decrease in alpha power during the application of TENS could be explained by the organization of pain-related cortical areas[24, 25]. Studies have reported attention-related decreases in alpha power over the parietal cortex in the absence of a target stimulus. They employed a cue stimulus that immediately preceded the target. The cue stimulus predicted exactly when the target was going to appear, and the decrease in alpha activity occurred during the cue − target stimulus interval[26–29].

In our opinion, the TENS for breast cancer patient can be used as an alternative to other treatments, specially for intercostobrachial nerve pain. Because is eqsy to apply and there are few contra-indications, patients can be treated with TENS without major problems. Beside our data suggest that both types of TENS (acupuncture and burst) reduce the pain. Our results indicate the slight tendency of TENS acupuncture to provoque greater analgesia.

This results differs considerably from our experiment, in which TENS was not cued and was given at long, random inter-stimulus intervals and was, therefore, unpredictable. Hence, attention-related decreases in alpha in the absence of a stimulus may not occur under this condition. This implies that merely thinking about a painful stimulus will not elicit the same changes in alpha as presenting an actual painful stimulus. Our data suggests a somatotopic organization in the parietal cortex after TENS application. We conclude that TENS changed electrical activities in the cortical of patients with intercostobrachial nerve pain. There were no significant differences between TENS acupuncture and burst, and both types reduced the pain. We recommend new investigations in order to replicate these findings utilizing different times and phase of intercostobrachial pain to comprehend cortical phenomenon during TENS action.

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