Original Article

Cranial Electrotherapy Stimulation for the Management of Depression, Anxiety, Sleep Disturbance, and Pain in Patients With Advanced Cancer: A Preliminary Study

Sriram Yennurajalingam, MD, MS, FAAHPM, Duck-Hee Kang, PhD, RN, FAAN†, Wen-Jen Hwu, MD, PhD, Nikhil S. Padhye, PhD, Charles Masino, MS, Seyedeh S. Dibaj, PhD, Diane D. Liu, MS, Janet L. Williams, MPH, Zhanni Lu, MPH, and Eduardo Bruera, MD

Department of Palliative Care, Rehabilitation, and Integrative Medicine (S.Y., C.M., J.L.W., Z.L., E.B.), The University of Texas MD Anderson Cancer Center, Houston, Texas; Center for Nursing Research (D.-H.K., N.S.P.), University of Texas School of Nursing, Houston, Texas; Department of Melanoma Medical Oncology (W.-J.H.), University of Texas MD Anderson Cancer Center, Houston, Texas; and Department of Biostatistics (S.S.D., D.D.L.), The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Abstract

Context. Cranial electrotherapy stimulation (CES) is a safe modulation of brain activity for treating depression, anxiety, insomnia, and pain. However, there are no published studies in patients with advanced cancer (ACPs).

Objectives. The aim of the study was to determine the feasibility and preliminary efficacy of a four-week CES intervention on depression, anxiety, sleep disturbance, and pain scores. Concurrent salivary biomarker studies were conducted.

Methods. In this one group open label pre- and post-intervention study with a four-week CES intervention, ACPs with one or more of four moderate intensity (≥3/10) Edmonton Symptom Assessment Scale (ESAS) symptoms (depression, anxiety, sleep disturbance, and pain) were eligible. Adherence (0%–100%), satisfaction rates (0–10), and safety were assessed. ESAS, Hospital Anxiety and Depression Scale (HADS), Pittsburgh Sleep Quality Index, Brief Pain Inventory, and salivary levels (cortisol, alpha amylase, C-reactive protein, and interleukin-1β, and interleukin-6) were assessed from baseline to Week 4.

Results. Thirty-three of 36 patients (92%) completed the CES. Median (interquartile range) adherence CES use and satisfaction scores were 93% (89–100) and 10% (9–10), respectively, and the adherence criteria was met in the study. CES use was safe (no Grade 3 or higher adverse events). HADS anxiety ($P < 0.001$), HADS depression ($P = 0.024$), ESAS anxiety ($P = 0.001$), ESAS depression ($P = 0.025$), Brief Pain Inventory pain ($P = 0.013$), Pittsburgh Sleep Quality Index daytime dysfunction ($P = 0.002$), and medication use ($P = 0.006$) scores improved after four-week CES treatment.

Conclusion. In this preliminary study, we found that the use of CES was safe and feasible in ACP. The use of CES was associated with significant improvement of depression, anxiety, pain, and sleep scores. These findings support further studies of CES in ACP for symptom control. J Pain Symptom Manage 2018;55:198–206. © *2017 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.*

Key Words

Advanced cancer, cranial electrotherapy stimulation, depression, anxiety, sleep disturbance, cancer pain

Introduction

Patients with advanced cancer (ACPs) frequently experience poorly controlled symptoms such as pain, sleep disturbance, depression, and anxiety.[1–3] These symptoms significantly decrease patients' functioning and quality of life as well as negatively affect patients' families distress levels.[4–11] However, there are limited treatments that target these symptoms simultaneously.[12] Innovative interventions are needed to

†Deceased.

Address correspondence to: Sriram Yennurajalingam, MD, MS, FAAHPM, Department of Palliative Care and Rehabilitation Medicine, Unit 1414, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, USA. E-mail: syennu@mdanderson.org

Accepted for publication: August 23, 2017.

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0885-3924/$ - see front matter
http://dx.doi.org/10.1016/j.jpainsymman.2017.08.027

reduce the suffering and improve quality of life for patients and their families.[13,14]

Most clinical trials for symptom management have been focused on pharmacological interventions, but non-pharmacological interventions also can significantly contribute to symptom improvement.[1] Pharmacological interventions for pain, for example, have been effective to a certain degree, but their effects have been limited leaving a considerable gap to fill for optimal symptom management.[1,15,16] Similarly, reviews on antidepressant treatments have shown either no significant efficacy over placebo[17] or relatively small-to-moderate effects only in moderate or severe depression.[18,19] Among the non-pharmacological approaches, behavioral and educational approaches have shown to be effective in alleviating depression,[20,21] pain, sleep disturbance, and fatigue in patients with cancer.[22–24] However, these interventions require long training and consistent adherence to the intervention, demanding considerable energy and time from the patients. This demand can be burdensome and unacceptable to patients with severe symptoms such as ACPs. Hence, more interventions are needed to effectively manage these distressing symptoms promptly.

Cranial electrotherapy stimulation (CES) is a non-invasive therapy delivering a low level of electrical stimulation to the brain via small battery-operated device (2.5″×4″) using ear clip electrodes. CES is a safe modulation of brain activity and has been approved by the U.S. Food and Drug Administration for treating depression, anxiety, insomnia, and pain. However, none of these studies were conducted with ACPs.[25]

In addition, there are limited published data defining the biological mechanisms that mediate CES and symptom control. A recent review in Nature Reviews—Neurology suggested that the modulation of autonomic nervous system activities to be a fundamental mechanism of deep brain stimulation.[26] Empirical evidence indicates that 42% of the externally administered currents penetrate the entire brain, particularly along the limbic system,[27] and this may lead to the release of various neurotransmitters and downstream hormones.[27,28] In few early studies, CES was found to alter urinary free catecholamine levels,[29] increase plasma endorphin levels,[30] and decrease serum cortisol.[31] In addition, CES is believed to influence the limbic and autonomic nervous system, which are closely interconnected with the hypothalamic-pituitary-adrenal-immune axis, which in turn is associated with the pathobiology of symptoms including depression, anxiety, sleep disturbance, and pain.[32–37]

The aim of this preliminary study was to determine the feasibility and preliminary efficacy of a four-week CES intervention on depression, anxiety, sleep disturbance, and pain scores. In addition, concurrent biomarker studies (including salivary cortisol, alpha amylase, C-reactive protein [CRP], interleukin [IL]-1β, and IL-6) were explored.

Methods

The University of Texas MD Anderson Cancer Center (MDACC) Institutional Review Board approved the protocol, and all patients were provided a written informed consent.

Patients

Patients eligible to participate in the study were approached by the clinical research coordinator in outpatient clinics at MDACC in Houston, TX. To be eligible, the patients must have a diagnosis of advanced cancer and one or more of the four symptoms (depression, anxiety, sleep disturbance, and pain) at the follow-up visit to the clinic with average intensity of ≥3/10 on the Edmonton Symptom Assessment Scale (ESAS; a 0–10 scale). The following were the rationale for enrollment at follow-up visit: 1) at the initial visit, nearly 100% of patients are prescribed pain medication based on a well-established standardized MDACC palliative care clinic protocol[38] and 2) our clinic data suggest that although symptom severity significantly decreases with the prescribed pharmacological treatment by palliative care team, substantial levels of symptoms remain,[15] enabling the test of potential synergistic efficacy of the CES. Patients were excluded from the study if they were on systemic anti-inflammatory prescription medications; having a known mental illness (e.g., schizophrenia, bipolar disorder); having delirium (Memorial Delirium Assessment Scale (MDAS) score ≥7); participating in other structured behavioral intervention(s); pregnancy; presence of an implantable device (e.g., pacemaker); cancer of the head and/or neck or brain tumor or brain metastasis; a history of seizure disorder as a precautionary measure. Stable doses of psychoactive medications were allowed as long as there been no significant changes in past two weeks.

Study Design

For this study, we used one group open label pre- and post-intervention design with a four-week CES as an intervention.

CES Intervention

The CES intervention consisted of applying the CES device for 60 minutes daily for four weeks. The Alpha-Stim® M (Electromedical Products International, Inc., Mineral Wells, TX) device was used for CES intervention. The CES devices were preset at the same low subsensory level microcurrent of 0.1 mA (one on the dial) at the frequency of 0.5 Hz by the manufacturer. CES

intervention protocol was as follows: 1) the electrode pad of ear clips was moisturized using a conduction solution supplied to the patients; 2) ear clips were applied comfortably to the earlobes; 3) to initiate the intervention, the CES device button was turned on; 4) only one button was operable, and device starts to count down 60 minutes; and 5) at the completion of 60 minutes, device would automatically shut down. Instructions were given to use the CES device for 60 minutes per session daily for four weeks. The patients were provided a diary to keep a daily log of their use of the study device. The research coordinator reviewed treatment compliance and the daily logs with patient during the weekly phone calls as a part of the study assessments.

Data Collection

The research coordinator obtained consent of the eligible patients, and collected the baseline data which included the demographic characteristics such as age, gender, race, cancer type, cancer treatment, and Charlson comorbidity index. Consented patients received brief training about the use of portable device. Data of the assessment tools including ESAS, Hospital Anxiety and Depression Scale (HADS), Pittsburgh Sleep Quality Index (PSQI), Brief Pain Inventory (BPI) short form, and National Comprehensive Cancer Network (NCCN) Distress Thermometer were collected five times; at baseline before CES use, and at Weeks 1, 2, 3, and 4, until the four-week CES intervention was completed. Primary end point was assessed at the end of four weeks.

Saliva samples were collected at bedtime and on awake next morning once a week on the night of filling out weekly questionnaires and the morning after.

Assessment Tools

ESAS is a widely used and validated scale for symptom assessment in seriously ill people.[39,40] Patients rate the intensity of 10 symptoms on a 0–10 rating scale, 0 = no symptom to 10 = worst possible symptom.

HADS is a 14-item scale to measure anxiety and depression among patients in clinics on a four-point rating scale from 0 to 3. A review of more than 700 papers suggest a 0.67–0.93 reliability.[41,42]

PSQI measures sleep quality and disturbance over two weeks. The PSQI showed a diagnostic sensitivity of 89.6% to distinguish good from poor sleepers.[43,44]

BPI Short Form was designed to assess the severity of pain and impact of pain on daily functions in patients with chronic disease like cancer. Reliability has been 0.77–0.91.[45]

MDAS contains 10 items on a scale ranging from 0 = none to 3 = severe. This was completed by the interviewer. Cronbach α in cancer patients was 0.91,[46] and a score of ≥7 indicates delirium.

NCCN Distress Thermometer is an assessment tool, which was used to measure the effect of the cranial stimulation on symptom distress.

The Safety of CES was assessed by the research coordinator at baseline (before initiation of

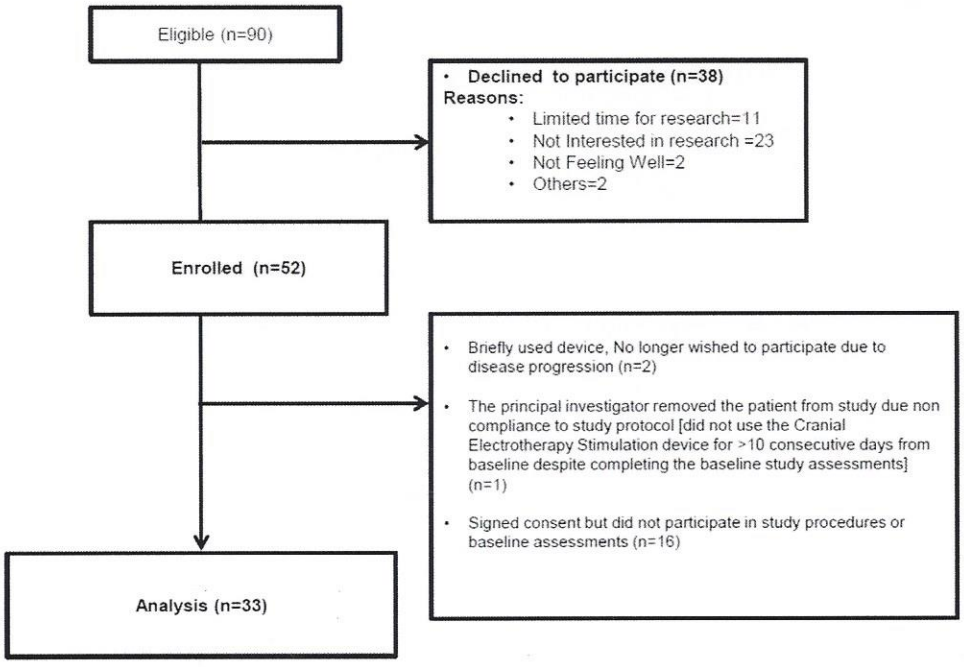

Fig. 1. Consort diagram.

treatment), treatment Days 8, 15, 22, 28, and 57 in accordance with the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.

Feasibility, Adherence, and Satisfaction with the CES was measured by monitoring the percentage of patients completing the study. The primary outcome of this study was feasibility. We defined the study feasible if 70% of patients were adherent to the study. Adherence was calculated by the percentage of (the number of days of CES use)/(prescribed days of CES use) using a log/record on CES use. Satisfaction was assessed with a three-item rating scale, 0–10 with 10 = most satisfied.

Biological Data

Salivary cortisol, alpha-amylase, CRP, IL-1β, and IL-6 were measured using specific immunoassay kits from Salimetrics, LLC (State College, PA). Salivary cortisol assay sensitivity is <0.003 μg/dL, and coefficients of variation for intra- and inter-assay precision are 3.4%–6.4%.[47–49] Salivary alpha-amylase (surrogate marker for sympathetic nervous system activity) has an assay sensitivity of <0.01 change in absorbance.[50,51] The salivary high-sensitivity CRP has a detection limit of 0.04 mg/L.[52] Salivary IL-1β assay sensitivity was 0.37 pg/mL.[53–57] The salivary IL-6 assay sensitivity was 0.7 pg/mL.

Statistical Analysis

The power was calculated using G*Power 3 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf)[34] for a repeated measures analysis of variance design to test difference of means between baseline and Week 4. Effect size for pain reduction was estimated to be $f = 0.19$ over a three-week period.[58] Setting $\alpha = 0.05$, power is 52% to detect a significant reduction of pain for a sample size of $n = 30$. Effect sizes for biological response variables are unknown, but the calculated sample size was sufficient to check the trend, yielding 36% power for an effect size as small as $f = 0.15$ or 75% power for a medium effect size, $f = 0.25$.

All demographic and clinical variables (e.g., age, gender, cancer type and treatment, medications) were summarized using descriptive statistics. Symptom scores and biomarker levels were compared between baseline and Week 4 using Wilcoxon signed rank test. All computations were carried out in SAS 9.3 (SAS Institute Inc., Cary, NC).

Table 1
Demographic Characteristics of Patients

Items	Total
Age	($N = 52$)
Median (IQR)	59 (47, 67)
Gender, *N* (%)	
Female	32 (63%)
Race, *N* (%)	
Asian	1 (2.0%)
Black or African American	1 (2.0%)
Caucasian	43 (84.3%)
Hispanic	5 (9.8%)
Native American	1 (2.0%)
Charlson comorbidity index	
Median (IQR)	9.0 (7.0, 10.0)
Primary diagnosis, *N* (%)	
Breast cancer	3 (6%)
Gynecologic cancer	6 (13%)
Gastrointestinal cancer	1 (2%)
Genitourinary cancer	3 (6%)
Melanoma	29 (60%)
Thoracic cancer	3 (6%)
Mesothelioma	1 (2%)
Sarcoma	2 (4%)
Receiving cancer treatment, *N* (%)	
Yes	19 (48.7%)
Receiving chemotherapy, *N* (%)	
Yes	15 (45.5%)
Receiving oral targeted medication, *N* (%)	
Yes	15 (45.5%)
Receiving radiation therapy, *N* (%)	
Yes	10 (30.3%)
Items	**Median (IQR)**
Baseline Symptoms ($N = 52$)	
ESAS pain	3.0 (1.0, 5.0)
ESAS fatigue	5.0 (3.0, 6.0)
ESAS nausea	0.0 (0.0, 2.5)
ESAS depression	2.0 (0.0, 6.0)
ESAS anxiety	4.0 (3.0, 7.0)
ESAS drowsiness	3.0 (1.0, 6.0)
ESAS dyspnea	0.0 (0.0, 4.0)
ESAS appetite	3.0 (0.0, 5.0)
ESAS sleep	5.0 (3.5, 6.5)
ESAS feeling of wellbeing	4.0 (2.0, 6.5)
ESAS symptom distress score[a]	28.5 (17.5, 42.0)
HADS anxiety	8.5 (6.0, 11.0)
HADS depression	7.0 (4.0, 8.0)
PSQI total score	10.0 (7.0, 14.0)
PSQI sleep quality	1.0 (1.0, 2.0)
PSQI sleep latency	2.0 (1.0, 2.0)
PSQI sleep duration	0.0 (0.0, 1.0)
PSQI habitual sleep	1.0 (0.0, 3.0)
PSQI sleep disturbances	2.0 (2.0, 2.0)
PSQI use of hypnotic and/or sedative medications	2.5 (0.0, 3.0)
PSQI daytime dysfunction	1.0 (1.0, 2.0)
Brief Pain Inventory severity	4.0 (1.3, 4.8)
Brief Pain Inventory interference	3.5 (0.8, 5.9)
NCCN distress thermometer score	5.5 (4.0, 8.0)

IQR = interquartile range; ESAS = Edmonton Symptom Assessment Scale; HADS = Hospital Anxiety & Depression Scale; PSQI = Pittsburgh Sleep Quality Index; NCCN = National Comprehensive Cancer Network.
[a]Sum of the score of pain, fatigue, nausea, depression, anxiety, drowsiness, dyspnea, appetite, and feeling of wellbeing.

Results

Figure 1 shows the consort diagram. Thirty-three of 36 patients (92%) completed the study after starting the intervention. Median (interquartile range) adherence for days with 60 minutes CES use was 0.929 (0.893–1.00), and the adherence criteria was met in the study. The median number of CES sessions among participants who completed 60 minutes of use per session was 27 (25–28) over four weeks, and the total minutes of CES use was 1613 (1500–1680).

Table 1 shows demographic characteristics of the study participants ($n = 52$). Nineteen of 33 patients (57%) were on 15 different types of centrally acting medications. Fourteen patients were on one type of centrally acting medication and five patients were on two different centrally acting agents. The following were the medications and their dose ranges (mg): carbidopa/levodopa (30/300), alprazolam (1), amitriptyline (10), citalopram (20–40), duloxetine (30–60), eszopiclone (3), fluoxetine (20), mirtazapine (7.5–30), nortriptyline (25), primidone (500), sertraline (100), temazepam (15–30), trazodone (50), venlafaxine (37.5–75), and zolpidem (18.75).

The number of patients who achieved 25% and 50% decrease, respectively, in symptom intensity and distress after CES treatment were as follows: depression (HADS) 56%, 53%; anxiety (HADS) 56%, 28%; sleep quality (PSQI) 41%, 21%; pain severity (BPI) 52%, 21%; distress scores (distress thermometer) 53%, 35%.

Table 2 shows significant improvement of HADS anxiety ($P < 0.001$), HADS depression ($P = 0.024$), as well as ESAS anxiety ($P = 0.001$) and ESAS depression ($P = 0.025$) scores. BPI pain ($P = 0.013$), PSQI daytime dysfunction ($P = 0.002$), and medication use ($P = 0.006$) scores also improved significantly after four-week CES treatment. Table 3 shows no significant change in the salivary cortisol, alpha-amylase, CRP, IL-1β, and IL-6 levels after four weeks of CES.

There were four Grade 3 or more adverse events reported (anemia, colitis, hepatic, and renal failure). None of these adverse events were related to CES use.

Table 4 shows that the median (interquartile range) satisfaction scores (0 = not satisfied; 10 = fully satisfied) for the CES use were 10 (9, 10) for each of three items.

Discussion

This study was first to evaluate feasibility and preliminary efficacy of an innovative non-pharmacological treatment approach (CES) on depression, anxiety, sleep disturbance, and pain in ACPs. We evaluated symptoms that are part of common symptom cluster experienced by many ACPs (depression, anxiety, pain, and sleep).[12,59–61] We found that the use of CES was feasible for treatment of symptoms in ACPs and was associated with significant improvement of anxiety depression, pain, PSQI daytime dysfunction, and hypnotic and/or sedative medication use after four-week CES treatment.

Table 2
Differences in Symptom Intensity Between Baseline and Week 4 ($n = 33$)

Variable	Median Change (IQR)	Test Statistic	*P*-value
ESAS			
Pain	0.00 (−1.00, 1.00)	−4	0.894
Fatigue	0.00 (0.00, 3.00)	39.5	0.205
Nausea	0.00 (−1.00, 1.00)	8.5	0.745
Depression	**1.00** (0.00, 3.00)	**86**	**0.025**
Anxiety	**2.00** (0.00, 4.00)	**132.5**	**0.001**
Drowsiness	1.00 (−1.00, 3.00)	62	0.160
Shortness of breath	0.00 (−1.00, 1.00)	6.5	0.803
Appetite	0.00 (−1.00, 1.00)	9.5	0.778
Sleep	1.00 (0.00, 2.00)	73	0.113
Feeling of wellbeing	1.00 (−1.00, 2.00)	59	0.155
SDS	6.00 (−2.50,18.00)	−1.764	0.078
PSQI			
PSQI total	2.00 (−2.00, 6.00)	79	0.055
Sleep quality	0.00 (0.00, 1.00)	26	0.161
Sleep efficiency	0.00 (0.00, 1.00)	22.5	0.326
Sleep daytime dysfunction	**0.00** (0.00, 1.00)	**141.5**	**0.002**
Use of hypnotic and/or sedative medication	**0.00** (0.00, 2.00)	**42**	**0.006**
Sleep disturbances	0.00 (0.00, 1.00)	21	0.119
Sleep duration	0.00 (0.00, 0.00)	11.5	0.477
Sleep latency	0.00 (0.00, 1.00)	17.5	0.329
BPI			
Pain severity	**1.00** (0.00, 2.00)	**100**	**0.013**
Pain interference	0.14 (−0.71, 1.43)	61.5	0.165
Distress thermometer			
Distress score	1.00 (−1.00, 3.00)	31	0.078
HADS			
Anxiety	**2.50** (0.50, 5.50)	**163.5**	**<0.000**
Depression	**1.50** (0.00, 3.00)	**107.5**	**0.024**

IQR = interquartile range; ESAS = Edmonton Symptom Assessment Scale; SDS = sum of the score of pain, fatigue, nausea, depression, anxiety, drowsiness, dyspnea, appetite, and feeling of wellbeing; PSQI = Pittsburgh Sleep Quality Index; BPI = Brief Pain Inventory; HADS: Hospital Anxiety & Depression Scale. Bold values indicate $P < 0.05$.

Table 3
Baseline and Differences in Salivary Biomarkers Between Baseline and Week 4 ($n = 33$)

Variable	Baseline, Median (IQR)	Median Difference	Test Statistic	*P*-value
Alpha amylase, U/mL AM	70.6 (39.2, 139.6)	5.74 (−21.36, 44.65)	18.5	0.648
Alpha amylase, U/mL PM	108.1 (54.3, 149.5)	0.44 (−42.57, 30.83)	1	0.982
Cortisol, μg/dL AM	0.3 (0.1, 0.5)[a]	0.01 (−0.11, 0.24)	18.5	0.648
Cortisol, μg/dL PM	0.1 (0.0, 0.1)	−0.02 (−0.12, 0.04)	−36	0.371
C-reactive protein, pg/mL AM	5982.8 (2838.8, 16,456.5)[a]	128.12 (−2225.02, 3235.99)	8.5	0.834
C-reactive protein, pg/mL PM	5048.0 (2477.9, 10,538.8)[a]	170.77 (−2710.31, 2965.63)	5	0.912
IL-1, pg/mL AM	385.1 (116.9, 839.6)[a]	−149.03 (−320.81, 98.43)	−66.5	0.092
IL-1, pg/mL PM	209.0 (106.5, 442.7)[a]	−37.90 (−407.85, 119.03)	−50	0.262
IL-6, pg/mL AM	11.1 (3.4, 30.8)[a]	−1.65 (−13.67, 2.80)	−45.5	0.116
IL-6, pg/mL PM	9.4 (4.1, 29.2)[a]	3.11 (−1.79, 10.49)	20.5	0.518

IQR = interquartile range; IL = interleukin.
[a]Above normal value.

Although there are no published studies in ACPs or patients in the palliative care setting,[25] there was a prior published randomized control study in early breast cancer patients. In this study, the authors found that the use of CES for three weeks was associated with lower depression scores compared with sham and control groups.[62] However, the symptoms were not severe at baseline so the study was not able to detect significant differences at the primary end point due to floor effect. Findings of our study suggest that it is feasible and safe to use CES in ACPs. A well-designed double blind, three-arm randomized controlled trial (CES arm, sham CES arm, and control arm) is needed to determine the effectiveness of CES on depression and its related symptoms in ACPs.

Numerous published reviews support the efficacy of CES on various symptoms in non-cancer patients. For depression, a meta-analysis of 20 studies indicates that CES is effective in decreasing depression in a variety of patients (e.g., psychiatric patients, fibromyalgia) with the mean effect size of $r = 0.50$. A meta-analysis of randomized controlled trials compared with the sham CES suggests similar efficacy of CES in anxiety.[63–65] Results of our study were consistent with the previous studies with more robust improvement of anxiety and depression scores. Reviews suggest the efficacy of CES in improving sleep disturbance.[27,66] In our study, we found improvement of PSQI total sleep score by two points, $P = 0.055$ (which was better than most previously published pharmacological trials), as well as significant improvement of PSQI daytime dysfunction and sedative medication use.[67,68] Further well-controlled studies are needed.

In our study, we found significant improvement in the pain scores at end of four weeks of CES intervention compared with baseline. These data are consistent with the data in non-cancer patients.[27,58,69–71] Prior studies also found that anxiety, depression, and pain was associated with disturbance in sleep.[72,73] In our study, we also found improvement of PSQI total sleep score by two points, $P = 0.055$ (which is better than most pharmacological trials). We also found significant improvement of PSQI daytime dysfunction, sedative medication use, anxiety, depression, and pain scores. Future well-designed studies need to validate these findings and target these symptoms as a cluster.

Our study did not find any significant change in the salivary cortisol, alpha-amylase, CRP, IL-1β, and IL-6 levels (except for a trend toward improvement of an IL-6 levels, $P = 0.0915$) after four weeks of CES. This could be explained because of the small sample size. Future well-powered studies are needed.

The main limitation of our study was the lack of sham control group. However, the results of our study showed that the CES use did show significant improvement of depression anxiety (target symptoms) rather than all the ESAS symptoms which usually occurs with use of placebo interventions.[74] Our findings in this study should be confirmed with a well-designed sham-controlled randomized-controlled trial before any conclusions regard to the role of CES as a potential intervention for the management of depression, anxiety, pain, or sleep disturbance in ACPs. Our preliminary findings regard to feasibility, adherence, and efficacy provide justification of such studies. However, we measured all the medications at baseline and expected the patients to be on stable doses. We have not measured the extra doses of analgesics the patients have been taking and this might be a limitation in the interpretation of the results. Future studies should be measuring these variables prospectively.

Table 4
Satisfaction With the Use of Cranial Electrotherapy Stimulation Device[a]

Satisfaction Scale Variables	Median
Difficult to use ($N = 33$)	10.00
Complicated to use ($N = 33$)	10.00
Unsatisfactory to use ($N = 33$)	10.00

[a]Visual analogue scale to assess the use of the device itself, regardless of its effects on symptoms (0 = difficult, complicated, or unsatisfactory; 10 = easy, simple, or satisfactory).

Conclusions

In this preliminary study, we found that the use of CES was feasible and associated with improvement in depression, anxiety scores (both HADS as well as ESAS anxiety and depression scores), BPI pain severity, PSQI daytime dysfunction, and sedative medication use scores.

Disclosures and Acknowledgments

The authors thank Electromedical Products International, Inc., Mineral Wells, TX (Alpha-Stim® M); Dr. Duck-Hee Kang and Biosciences Laboratory, Center for Nursing Research, University of Texas School of Nursing, Houston, TX (salivary biomarkers analysis); and Department of Melanoma Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX (patient referral).

All authors have no conflicts of interest.

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