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

Yennurajalingam S, Kang D-H, Hwu W-J, Padhye NS, Masino C, Dibaj SS, Liu DD, Williams JL, Lu Z, Bruera E. Cranial electrotherapy stimulation for the management of depression, anxiety, sleep disturbance, and pain in patients with advanced cancer: a preliminary study. *Journal of Pain and Symptom Management.* 2018 Feb; 55(2): 198-204.

Device

Alpha-Stim®

Key Variables

Pain, Anxiety, Depression, Insomnia, Functionality, Medication Use

Objective

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.

Design

This study was an open label pre and post-intervention study with a four-week CES intervention. The subjects were recruited from the patient population at MD Anderson Cancer Center in Houston Texas, and were considered advanced cancer patients.

Primary Effectiveness Endpoint

Brief Pain Inventory (BPI) and adherence to the treatment with a >70% adherence rate considered significant.

Secondary Effectiveness Endpoint

Edmonton Symptom Assessment Scale, Hospital Anxiety and Depression Scale, Pittsburgh Sleep Quality Index, NCCN Distress Thermometer and medication usage.

Key Inclusion Criteria

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).

Key Exclusion Criteria

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.

Protocol Summary

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.

Outcome Measures

ESAS is a widely used and validated scale for symptom assessment in seriously ill people. 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.

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

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.

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

Analysis

The power was calculated using G*Power 3 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. 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).

Results

Pain

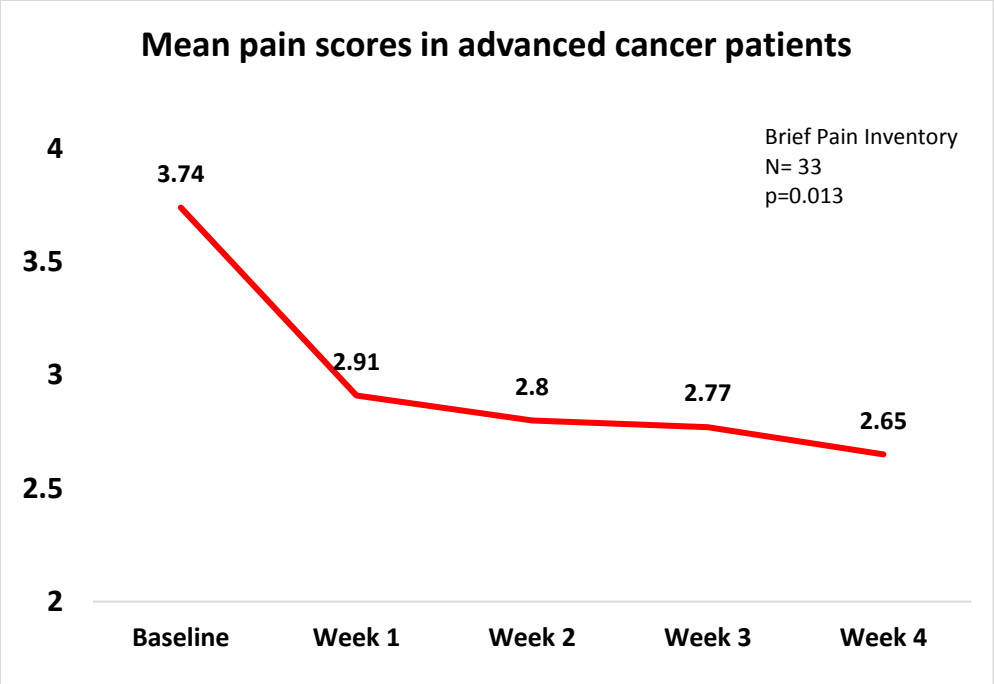

Figure 1. Mean pain scores in advanced cancer patients

Anxiety

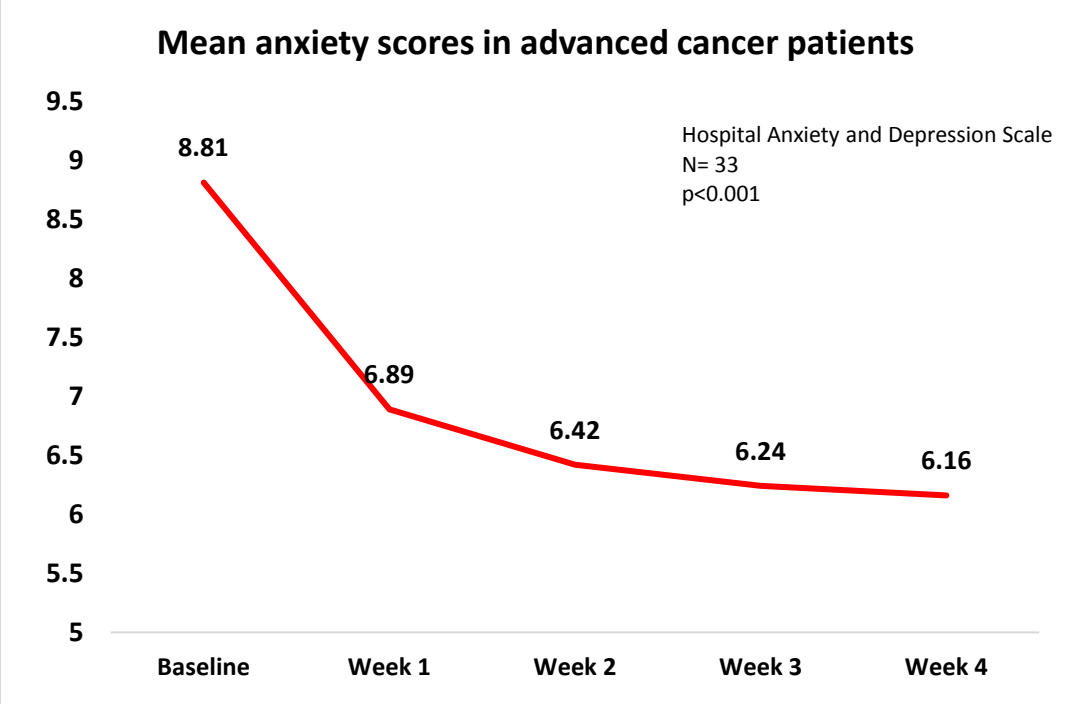

Figure 2. Mean anxiety scores in advanced cancer patients.

Depression

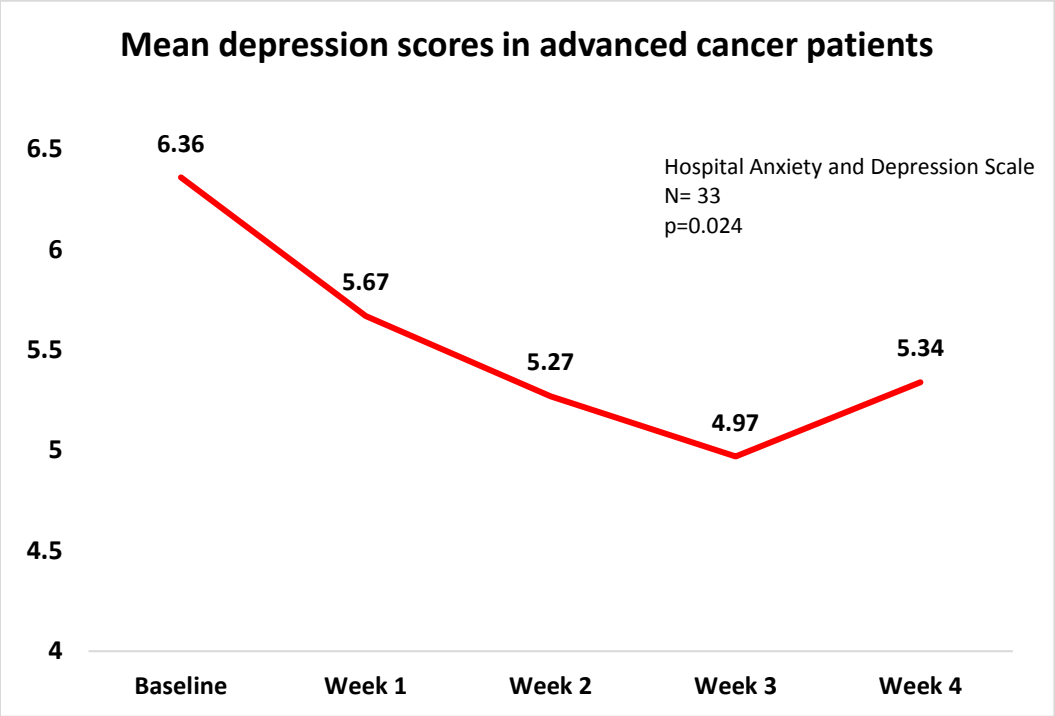

Figure 3. Mean depression scores in advanced cancer patients

Insomnia

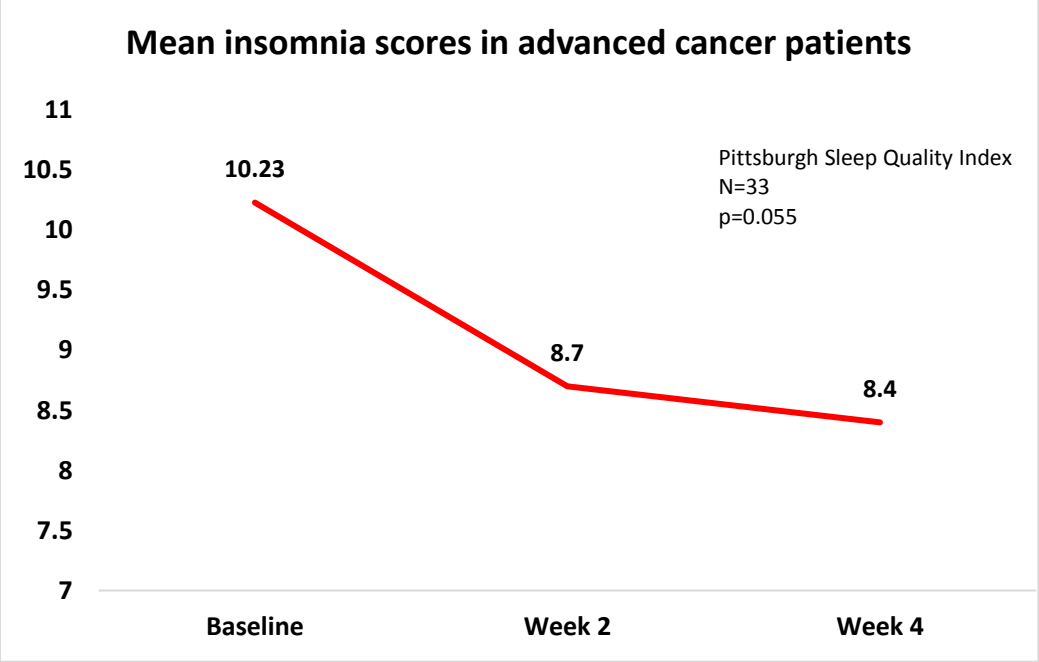

Figure 4. Mean insomnia scores in advanced cancer patients

Conclusion

The study found significant improvement in the pain scores at end of 4 week of CES intervention compared to baseline. The study also found improvement of PSQI total sleep score by 2 points, p=0.055 (which is better than most pharmacological trials). The researchers also found significant improvement of PSQI daytime dysfunction, sedative medication use, anxiety, depression, and pain scores.

Researchers concluded by saying that the use of cranial electric stimulation (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.