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Use of Bioelectric Stimulation for the Treatment of Hypertension: A Pilot Study

Introduction: In the United States approximately 80 million Americans have hypertension (1). In Brazil, hypertension affects 32.5% (36 million) of the adults, including over 60% of the elderly, contributing direct or indirectly to 50% of the deaths due to cardiovascular disease (CVD) or Stroke. In 2013 there were 1,138,670 deaths, 339,672 of which (29.8%) due to CVD, the major cause of death in Brazil (2). Along with DM, its complications (cardiac, renal and stroke) have high impact on loss of work productivity and on family income, estimated as US$ 4.18 billion from 2006 to 2015.

Currently, non-pharmacological therapeutic methods are being used to treat resistant hypertension (RH). These are invasive, require long term follow up to monitor the results and may cause unwanted complications during and after the procedure, besides being expensive(3). These interventions and devices have yet to show the ability to reduce the dose or number of medications needed to control hypertension.

Transcutaneous electrical nerve stimulation (TENS) has been a useful modality for pain control (4) since the gate control theory was introduced by Melzack & Wall (5). BES has also shown to be effective in the reduction of sympathetic activity in healthy subjects and individuals with cardiovascular diseases. This form of neuromodulation is being used to treat a wide variety of medical conditions. In healthy subjects, sympathetic activity decreases (6) after low-frequency BES. In addition, patients with hypertension show a reduction of Blood Pressure (BP) after low frequency BES (7),(8) and, in heart failure patients, BES decreases sympathetic activity (9) largely as evidenced by reduction in heart rate.

Study Goal:

The goal of this study is to compare the use of TENS therapy to improve blood pressure control when applied to the paravertebral area between C7-T4 alone, or this location plus additional stimulation sites including wrist, ankle, and ear lobe.

Study design: Prospective, randomized, 2 arm, open label, controlled trial

Target Subjects: Patients with a diagnosis of essential hypertension.

Number of Patients to be Enrolled: 30

Number of study sites: 2-4

Duration of Study: 4 weeks

Number of Treatments: 10

Frequency of Treatments: 3 x's/week for 2 weeks, then 2x's/week for 2weeks

Duration of Each Treatment: 30 minutes

Inclusion criteria:

Age: 20-75 years

Sex: male or female

Documented hypertension: systolic blood pressure (SBP) > 150 mm Hg and/or Diastolic Blood Pressure (DBP) > 90 mm Hg on at least two measurements in a physician office.

Exclusion criteria:

Myocardial infarction past 3 months

History of stroke in past with residual neurologic deficit

Active smoking

Change in drug therapy in the 2 months preceding the study.

Serum Creatinine > 2.5 ng/ml or GFR < 30 ml/min

Baseline BP recording:

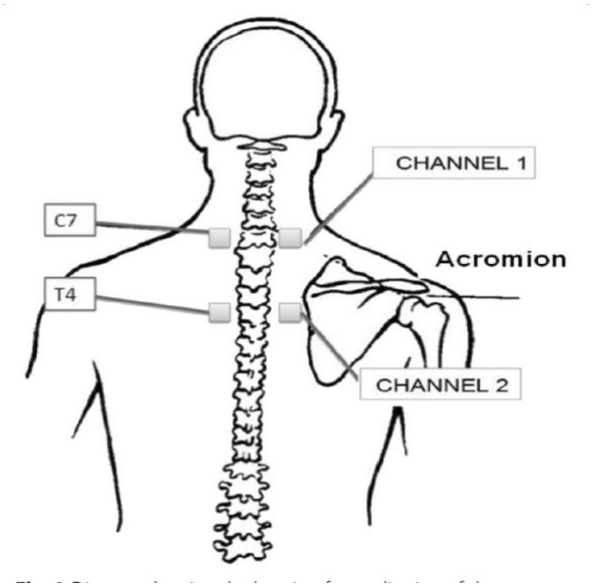
Each subject will have a 24 hr ambulatory blood pressure monitor placed with automatic cuff inflation every 15 minutes from 8 AM-10 PM, and every two hours from 10 PM-8 AM to establish the baseline BP control with mean, peak, and lowest BP recorded.

Treatment Arms:

Eligible subjects will be randomly assigned by electronic randomization (www.randomization.com), to the one of three groups of 10 patients each:

Group 1 Cervical Paravertebral Stimulation:

- TENS will be applied bilaterally in the cervicothoracic ganglion region located between the C7 and T4 vertebral processes for 40 min three times weekly for a total of 4 weeks. (Figure 1)



CERVICAL PARAVERTEBRAL

Group 2 Cervical Paravertebral, Plus Ear, Wrist, and Ankle Stimulation

- TENS will be applied in the cervicothoracic ganglion region located between the C7 and T4 vertebral processes, plus wrist and ankle via electrodes provided by the sponsor for 30 min three times weekly for a total of 4 weeks.

Group 3: Stimulation of the kidney alone with electrodes anterior and posterior to both kidneys to target increase in circulating levels of the protein Klotho

PAIRED ELECTRODES ON THE BACK OVER KIDNEYS

Application of treatment electrodes:

- Adhesive electrodes measuring 9x5 cm will be placed on the bilateral paravertebral region of the spine region from C7-T4
- Before the application of TENS (METTLER DEVICE), the skin site for the current application will be cleaned with alcohol to avoid any barrier conduction of the electrical current.

Stimulator to be used: FDA and CE Mark approved Mettler 240 desktop stimulator.

PROTOCOL:

Patients will rest for 15 minutes and, during the first treatment period will fill out the evaluation form, which contains identification data and questions about the patient's clinical status, such as weight and height. Before and after the intervention, blood pressure and heart rate over one minute will be measured. The micro-current from the stimulator will be delivered at patients selected sensory-level intensity, adjusted every 5 minutes by the sensory threshold as tolerated by each subject, but with no motor contraction or pain reported. The sessions will take place at the same time of the day throughout the protocol.

The participants will be comfortably accommodated in an acclimatized room (23.C) in supine position, with head elevation of 30° and knees resting on a wedge. All participants will be asked to not perform exhaustive exercises and ingest caffeine at least twelve hours before the intervention, and they were **instructed to have a meal before the assessment.**

END POINTS:

Arterial Blood Pressure

Blood Pressure (BP) will measured by 24 hour recording before and at the end of the study, as well as at each treatment session as proposed by the VI Brazilian Guidelines on Hypertension (2), with an automatic calibrated device, model HEM-705CP (Omron Healthcare Inc., Illinois, USA), and the cuff adjusted for arm circumference. The subject will be seated and three measurements will be obtained. Then the respective mean value will be calculated, which was used in the data analysis.

Heart Rate Variability(THIS IS NOT RELATED TO BP CONTROL BUT SEEMS POSSIBLE TO INCLUDE

The analysis of autonomic control will be performed by means of a sensor placed on the patient's middle finger and connected to a Finapres device (Ohmeda 2300, Colorado, USA), which recorded blood heart rate beat to beat. Then, the signal conversion will be performed using PowerLab (Power Chart).

The analysis wwill be carried out using the Kubios 2.0 software (Biosignal Analysis and Medical Imaging Group, Kuopio, Finland). For the analysis of heart rate variability (HRV), RR intervals were obtained from the continuous ECG signal recorded by the Finapres device. The time series of RR intervals will be analyzed in time and frequency, and variability parameters and autonomic balance obtained. In the time domain, we will calculate the mean values of RR intervals, standard deviation, and the square root of the

sum of the square of successive differences (rMSSD). The signal will be acquired immediately before and after the interventions, for a 10-minute period. The outcome variable consisted of the analysis of the HRV performed by an individual blinded to the subject's group assignment. The time series obtained from the tachogram, related to each selected segment, were quantitatively evaluated considering heart rate (HR) values, total and normalized powers (n.u) of low-frequency (LF – 0.04 to 0.15 Hz) and high-frequency (HF – 0.15 to 0.40 Hz) components of HRV, and the sympatho-vagal index (LF/HF). Normalized units (n.u.) were obtained by dividing the power of a given component by the total power (from which VLF has been subtracted), and multiplying it by 100 (10).
BEFORE AND AT END OF 4 WEEKS FOR BEST EVALUATION

Statistical Analyses

The normality of the variables was verified by the Shapiro-Wilk test. Changes were made to variables that did not meet this assumption, such as natural logarithm, square root and reverse. For normally distributed variables, analyses of variance (ANOVA) were performed at baseline and post intervention, and Kruskal-Wallis tests will be used for variables that did not meet the assumption. The comparison between moments will be carried out using Student's t test or Wilcoxon as the distribution of variables. A P- value of <0.05 will be considered statistically significant for all tests. All analyses will be performed with the SPSS 22.0 software (SPSS, Chicago, IL, USA).

Primary outcome measure: BLOOD PRESSURE

The primary outcome measure will be the change from baseline in the mean peripheral blood pressure by 24 hour monitor of individuals with resistant hypertension after transcutaneous electrical nervous stimulation using the three different electrode placements of paravertebral and the combination of ankle and wrist, and kidney placement of electrodes.

Secondary outcome measures:

Heart Rate Variability

The mean heart rate at rest and variability over 24 hours will be calculated and compared between the three treatment arms.

Arterial Stiffness

The secondary outcome measures from baseline are the arterial stiffness measurement parameters (including central blood pressure) of individuals with resistant hypertension after transcutaneous electrical nervous stimulation. NOTE: There is no text to describe the method of measuring arterial stiffness-? Delete

Adverse events: The adverse events will be investigated by open questions at the time of each treatment session, which will address general symptoms and the presumed adverse effects of the electrostimulation used in the trial. Laboratory adverse events, such as metabolic changes and inflammatory markers, will be investigated at the final visit of the participants.

Missing or dropout: Participants will be registered with a phone number and address for further contact in case of missing outlined visits. The investigator is allowed to enroll additional subjects for any subject that fails to complete the entire course of 10 treatments and drops out early. Additional patients beyond the planned total of 30 subjects, with 10 Subjects/group, can be added at the agreement of the sponsor and investigator.

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