CLINICAL SUMMARY: HEMODYNAMICS

The Neuro-Stim System (NSS-2) peri-auricular cranial nerve field neuro-modulating stimulation device was performed on a cohort of 12 healthy adult patients over a 3-week span. A Transcranial Doppler (TCD) was used to assess intracranial hemodynamic changes including fluid velocity, Pourcelots resistivity index (RI) and Gosling's pulsatility index (PI) in the middle cerebral, anterior cerebral, posterior cerebral, basilar, and vertebral arteries. Upon peri-auricular neuro-modulating stimulation by the NSS-2, the mean hemodynamic flow in the cerebral arteries indicated a

compensatory response, increasing by 1-19%, while the PI and RI values decreased by 2-11% from the baseline. The study indicates that NSS-2 peri-auricular stimulation decreases the flow resistance and increases the cerebral perfusion.

Methods

A cohort of 12 subjects, ages 19-64, were randomly recruited. The subjects were interviewed individually. Past medical and surgical histories were collected and screened for potentially disqualifying morbidities. All subject's questions were answered to the subject's satisfaction.
Informed consents were signed. Patients were appointed individually at the test site. Upon arrival, the subjects were informed of the nature of the study.

For each subject, the chosen ear was disinfected with a 70% isopropyl alcohol pad and left undisturbed for 10 minutes. After 10 minutes, the baseline TCD assessment of the blood flow in the middle cerebral (MCA), anterior cerebral (ACA), and posterior cerebral (PCA) vertebral arteries was performed. Each TCD ultrasound assessment involved measuring the blood flow (mean, peak systolic, and end diastolic) velocities and the downstream cerebral resistance using Gosling's Pulsatility Index (PI) and Pourcelots Resistivity Index (RI). Following the disinfection protocol and TCD procedure, pre-sham data was collected and recorded.

A sham device was placed and TCD measurements were taken 10 minutes after placement. Following data collection, an active device was placed in a similar way. After 10 minutes of active stimulation, TCD measurements of blood flow were collected. Following device removal the subject was released from the study.

Results

Percentage changes in blood flow velocity were found to be +18.7%, +1.0%, and +12.0% in the ACA, PCA, and MCA with an activated NSS-2 device implanted over a 10-minute period, respectively. Over the same period, the PI and RI decreased by 10.9% and 5.9% in the ACA blood flow, respectively. In the MCA and PCA, the RI values decreased by 2.0% and 9.0%, respectively. The PI in the PCA decreased by 3.7% and that in the MCA by 1.7%. Increase in blood flow is a direct result of parasympathetic stimulation via the vagus nerve. Increase in cerebral perfusion affects neuropathy and cellular repair, all of which affect pain management both centrally and peripherally. Our findings indicate that peri-auricular implantation of the NSS-2 stimulates the cranial nerves anatomically located in the peri-auricular area directly affecting the extrinsic perivascular innervation, as well as the micro-vascular bed, of the intracranial arteries to decrease flow resistance and increase cerebral perfusion.

OVERALL CONCLUSION

The Neuro-Stim System stimulates the vagal system which, in turn, increases perfusion which alters neuropathy. TCD measurements after using the NSS-2 verify increases in cerebral perfusion and controlled studies with the NSS-2 have demonstrated reduction in acute and chronic pain associated with a variety of common conditions. A review of device use and associated adverse events support the safety of the device

-FULL STUDY DETAILS AVAILABLE UPON REQUEST-

Neuro-Stim Overview and Relation to Study

The Neuro-Stim System (NSS-2) is a battery-powered, externally applied generator with four-wire leads of which three are attached to electrode/needle arrays and one is attached to a single point needle. The generator is located behind the ear and produces electrical stimulation impulses which are transferred via an electrode/needle array to branches of cranial and/or occipital nerves and sympathetic fibers of the arterial branches. electrode arrays are designed to decrease sympathetic stimulation of targeted neuro-vascular bundles. A medical penlight is provided with the system to aid in Transillumination of the vascular bundles for electrode placement. Optimal placement of the NSS-2 arrays is near but not on a main arterial branch (within .5-2 mm of the vascular branches) so proper energy transfer is completed in accordance with Ohm's and Coulomb's laws[1].

Preclinical studies have elucidated how Percutaneuos Electrical Nerve Field Stimulation (PEFNS) decreases the perception and sensation of pain and dampens the signs and symptoms of opioid withdrawal.

The limbic system is a key component of the CNS that links stress, anxiety and pain from the somatic or visceral structures. The amygdala in particular, integrates information regarding fear, anxiety and pain and facilitates the individual phenotypic responses. In fact, studies have shown that hyperactivity of neurons in the amygdala occur in chronic pain conditions regardless of whether the pain is originating form somatic or visceral structures[2,3]. The initial hypothesis by Miranda et al. regarding the mechanism of PENFS was that diminishing the firing of these neurons would change brain connectivity and alter the response to pain regardless of whether it was
visceral or somatic. This hypothesis was proven in the preclinical animal study using both behavioural and electrophysiology experiments[4]. In that study, there was an increase in somatic hypersensitivity that resulted from a visceral insult (colitis). Decreasing the firing of neurons in the amygdala through PENFS led to a significant decrease in both somatic and visceral pain. This hypothesis was also supported by a clinical trial with documented improvements in functional abdominal pain[5,6]. A somewhat surprising result from the pre-clinical study was the significant attenuation of spinal cord neurons after PENFS which also contributes to decreasing the pain response.

The central nucleus of the amygdala is also the output nucleus of the amygdala and has major projections to the forebrain and brainstem through which it also influences spinal neurons. Nociceptive drives entering the spinal cord from afferent signals (somatic or visceral) are modulated by brainstem nuclei including the RVM and PAG. These nuclei get input from the nucleus tractus solitarius (NTS), which is the first stop for PENFS signals[7,8]. Because the amygdala and NTS are modulated by PENFS, they are able to dampen spinal cord neurons through their effect on the brainstem[9,10,11]. This effectively decreases the transmission of pain impulses from visceral and/or somatic structures to supraspinal areas. This was evident in the animal studies where PENFS caused a significant decrease in the firing of lumbar spinal neurons[12]. Interestingly, deactivation of the amygdala not only inhibits the pain response but also modulates fear, autonomic responses and anxiety, all features seen during opioid withdrawal.

Patients suffering from withdrawal experience visceral pain (abdominal cramping), somatic pain (bone or joint pain), autonomic dysregulation (sweating, increased heartrate) as well as anxiety. The pain along with the aversive and anxiety-like state of withdrawal involves a stress response and the autonomic nervous system that are unequivocally linked to the amygdala[13,14,15]. Several studies have already demonstrated that the amygdala is involved in the negative, emotional state of withdrawal to opioids and drug craving[16,17]. It was interesting to note that it took approximately
15 minutes to see the attenuation of CNS neurons in the pre-clinical studies, which is approximately the same time it took to see a clinical response in patients with acute opioid withdrawal. Overall, limbic and spinal structures provide a common central link between a state

of chronic pain and opioid dependence and the reason why PENFS clinically improves visceral and somatic pain and decreases the signs and symptoms of opioid withdrawal.

Innovative Health Solutions (IHS) has sponsored two clinical studies of its Neuro-Stim System for acute and chronic pain management in different clinical conditions. These studies support the proposed Indications for Use of the system for the management of acute and chronic pain in subjects with conditions such as: pain associated with gastrointestinal disorders such as irritable bowel syndrome (NTC02367729)