CLINICAL SUMMARY: Gastrointestinal Pain

This was a double-blind, randomized, placebo-controlled study of the NSS-2 in juveniles age 11-18 who satisfied the criteria for a functional abdominal pain disorder (FAPD) including irritable bowel syndrome (IBS), functional dyspepsia, functional abdominal pain not otherwise specified (FAP-NOS) and abdominal migraine.

Methods

Subjects were required to have an average daily pain rating ≥ 3 (out of 10). The primary end point was determined using the validated tool of Pain Frequency-Severity-Duration (PFSD) scores. Treatment duration was 3 weeks with measurements conducted weekly. Results were statistically analysed with a p-value of < 0.05 considered significant.

One hundred fifteen subjects were enrolled with n=57 assigned to treatment and n=47 assigned to sham. Two subjects were subsequently excluded due to a change in diagnosis and nine subjects withdrew for either aesthetic reasons or being uncomfortable with the device.

Results

A greater improvement in pain was seen in the treatment group compared to sham for all 3 weeks ($p<0.001$); at week 3 the sham group had a median pain score of 7 vs a median pain score of 5 in the treatment group ($p<0.001$). Composite scores between the two groups were also significant at week 3 with a median in the sham group of 15.2 vs. 8.4 in the treatment group ($p<0.005$).

Using a ≥30% reduction in worst pain as a responder threshold, 60% of patients in the treatment group improved compared to 22% in the sham group at week 3 compared to baseline ($p<0.001$). Similarly, by week 3, 57% of patients in the treatment group had at least a 30% improvement in usual (average) pain scores from baseline compared to 29% in the sham group ($p< 0.007$).

Subjects rated their symptoms as better, worse or no change based on a 15-point scale: -7 to -1= worse; 0 = no change; +1 to +7 = better. A score of +2 was considered to be a significant improvement in global rating of symptoms. At the end of 3 weeks the sham group had a median score of +1 (range: -5 to 6). At the end of 3 weeks the treatment group had a median score of +3 (range: -3 to 7) representing a significant improvement in global rating of symptoms over sham ($p<0.001$).

Side Effects/Adverse Events

Six subjects reported ear discomfort, (n=4 treatment; n=2 sham). Three (3) subjects had adhesive reactions, 1 subject developed dizziness and nausea after device placement (treatment). One subject (sham) had an episode of syncope prior to placement of device that was later determined to be related to needle phobia.

Conclusion

Treatment with the Neuro-Stim device significantly improved worst pain and composite pain scores from baseline in all 3 weeks measured. There was also a significant improvement in the treatment group compared to sham using the responder definition of ≥30% improvement in weekly pain. Overall global symptoms improvement was significantly better in those with active treatment compared to sham. These results suggest that Neuro-Stim may be an effective non-pharmacological treatment option for patients with chronic abdominal pain.

MULTI STUDY 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. Cumulatively the clinical data collected, bolstered by the mechanism of action of the Neuro-Stim system, support the proposed Indications for Use for management of acute and chronic pain.

-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)