CLINICAL SUMMARY: Opioid Withdrawal

NOTE: BRIDGE® is a target market specific brand name for the Neuro-Stim device.

The study objective was to determine (1) the effects of the BRIDGE on withdrawal scores during the induction phase of opioid withdrawal therapy, and (2) the percentage of subjects who underwent successful withdrawal and transitioned to medication assisted therapy (MAT).

Methods

Adult patients treated with the BRIDGE during medically supervised withdrawal in outpatient clinics were included in this study. The clinical opioid withdrawal scale (COWS) scores were prospectively recorded during different intervals (20, 30 and 60 min) of treatment with the BRIDGE and analysed retrospectively. A subset of patients had scores recorded 5 days post BRIDGE. Those who returned to the clinic and received their first dose of maintenance medication were considered to be successfully transitioned. This study was a single-arm study with no control or placebo group due to ethical concerns. Given the rapid response to stimulation (15-30 minutes), the results are objectively evident.

Results

In this cohort (n=73), the mean COWS score prior to BRIDGE placement was 20.1 (±6.1). Twenty minutes after BRIDGE placement, the mean score was significantly reduced to 7.5 (±5.9) (62.7% reduction, $p<0.001$). The scores continued to decrease after 30 minutes 4.0 (±4.4) and 60 minutes 3.1 (±3.4) (84.6% reduction, $p<0.001$). No rescue medications were used during this period. **The mean withdrawal score on day 5 was 0.6 (97.1% reduction, $p<0.001$) (n=33)**. Overall, 64/73 patients (88.8%), successfully transitioned to MAT.

Conclusion

Neurostimulation with the BRIDGE is associated with a reduction in opioid withdrawal scores. This effect persisted during the induction period and allowed for effective transition to MAT.

-FULL STUDY DETAILS AVAILABLE UPON REQUEST-

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.

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)