Articles for Week:

Petersen EA, Stauss TG, Scowcroft JA, et al. Effect of High-frequency (10-kHz) Spinal Cord Stimulation in Patients With Painful Diabetic Neuropathy: A Randomized Clinical Trial. *JAMA Neurol*. 2021;78(6):687-698. doi:10.1001/JAMANEUROL.2021.0538

Petersen EA, Stauss TG, Scowcroft JA, et al. Durability of High-Frequency 10-kHz Spinal Cord Stimulation for Patients With Painful Diabetic Neuropathy Refractory to Conventional Treatments: 12-Month Results From a Randomized Controlled Trial. *Diabetes Care*. 2022;45(1):e3-e6. doi:10.2337/DC21-1813

Background and Overview:

Diabetes has a worldwide prevalence of 8.5% with approximately 20% of those patients developing painful diabetic neuropathy. Treatment includes neuropathic medications such as gabapentinoids, SNRIs, TCAs, and topical solutions. Prior systematic reviews and meta-analysis of these medications have shown a number needed to treat between 3.6 and 7.7 with a number needed to harm between 11.8 and 25.6. Prior to this study, there were only two randomized trials on treatment of PDN with SCS. These studies were limited to tonic, paresthesia-based stimulation[1].

Methods:

Trial design: Multicenter, randomized, prospective, open-label study
Key inclusion criteria: (1) Painful diabetic neuropathy of lower extremities for 12+ months, (2) refractory to treatment with a gabapentinoid and at least one other class of analgesic, and (3) lower limb average pain intensity ≥ 5/10
Key exclusion criteria: (1) Hb A1C > 10%, (2) BMI > 45, and (3) daily opioid usage > 120 MME
Control: CMM
Treatment: SCS with 10-kHz SCS plus CMM
Primary endpoint: 50% or greater pain relief based on VAS without worsening of clinical neurologic function at 3 months analyzed with intention-to-treat

Patients randomized to the SCS arm underwent a temporary SCS trial lasting 5-7 days using percutaneous leads placed epidurally spanning T8 to T11. Patients reporting 50% or more pain relief received a permanent SCS implant. Patients were followed for a total of 24-months with options for patients to crossover at 6-months[1]. Thus far, the 12-month outcomes[2] have been published and the 18-month outcomes were reported at a recent national neuromodulation conference.

Results:

1. 6-month Results[1]:
    a. 50% pain reduction:
        i. CMM: 5% responder rate at 6 months
        ii. SCS plus CMM: 79% responder rate at 6 months
    b. VAS pain reduction
        i. CMM: 7.0 at baseline to 6.9 at 6 months
        ii. SCS plus CMM: 7.6 at baseline to 1.7 at 6 months
2. 12-month Results[2]:
    a. 50% pain reduction:
        i. SCS plus CMM: 86% responder rate at 12 months
        ii. Crossover group: 84% responder rate at 6 months
    b. VAS pain reduction
        i. SCS plus CMM: 7.6 at baseline to 1.7 at 12 months
        ii. Crossover group: 7.2 at baseline with no change at 6 months with improvement to 2.0 at 12 months

Reflection:

Many would say that the past decade in neuromodulation has been defined by the innovation of novel waveforms that have improved efficacy and better patient satisfaction compared to the paresthesia-based, tonic stimulation that we offered in the decades prior. One of these novel waveforms has been subthreshold, 10 kHz stimulation. This waveform was studied in the SENZA-RCT[3,4] which compared the high-frequency stimulation with conventional stimulation in patients with back and limb pain. This trial started recruiting patients in 2012 and published their outcomes in 2015[3] and 2016[4], which showed superiority over conventional stimulation out to 24 months. Around this time, a couple other randomized trials, the PROMISE study[5] and the SUNBURST trial[6], were performed that also focused on patients with back and/or leg pain. However, these studies have not been able to identify specific pain etiologies that have best outcomes with spinal cord stimulation, although many patients appear to have failed back surgery syndrome and radiculopathy.

The SENZA-PDN[1,2] trial appears to be a key step in helping providers identify specific pain etiologies that will benefit from high-frequency spinal cord stimulation. It takes a similar step as that taken by the ACCURATE[7] study in 2017, which showed superiority of DRG stimulation over conventional SCS in treating CRPS. Two prior RCTs have demonstrated efficacy if SCS in PDN using conventional SCS that were published in 2014 and 2015[1]. This is the first time we have had a randomized trial studying one of the novel waveforms in PDN.

One of the secondary end points in the study was the patient's neurologic assessment. At six months, 62% of patients with 10 kHz stimulation showed improvements in their neurologic examination while only 3% of the control arm. These improvements were maintained at the 12-month mark and replicated in those that crossed over at the 6-month mark. Most of these improvements were attributed to sensory improvements. The authors mention that these changes were observed by the end of the SCS trial. These findings suggest that these high-frequency SCS may have a disease-modifying role beyond[1]. However, this will need to be studied further before such conclusions can be drawn.

This leads us to two of the limitations with this trial: industry-sponsorship and lack of blinding. To the best of my knowledge, the De Andres et al study (n = 60) published in 2017 is the only non-industry sponsored study comparing 10 kHz to traditional stimulation. This study showed that both high-frequency and traditional stimulation had effective analgesia, but did not show a superiority with high-frequency stimulation as shown in the SENZA-RCT on back and leg pain[8,9]. A second study sponsored by Stimwave, a competitor to Nevro, and published by Bolash et al in 2019, randomized 72 patients to receive either 10 kHz stimulation or low-frequency stimulation using the Stimwave Freedom SCS system[9,10]. This study demonstrated analgesic efficacy of both waveform without statistical superiority of high-frequency stimulation. However, it should be noted that the results from this study appear to trend towards better outcomes with high-frequency and may have been limited by a relatively smaller sample size compared to the SENZA-RCT.

Although the outcomes so far have been promising, it is important to ensure reproducibility and demonstrate durability of therapy. The 24-month data is expected to be published in fall of this year and we eagerly await those results.

Work Cited:

1. Petersen EA, Stauss TG, Scowcroft JA, et al. Effect of High-frequency (10-kHz) Spinal Cord Stimulation in Patients With Painful Diabetic Neuropathy: A Randomized Clinical Trial. *JAMA Neurol*. 2021;78(6):687-698. doi:10.1001/JAMANEUROL.2021.0538
2. Petersen EA, Stauss TG, Scowcroft JA, et al. Durability of High-Frequency 10-kHz Spinal Cord Stimulation for Patients With Painful Diabetic Neuropathy Refractory to Conventional Treatments: 12-Month Results From a Randomized Controlled Trial. *Diabetes Care*. 2022;45(1):e3-e6. doi:10.2337/DC21-1813
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Comments:

Lucas First, Fellow at Dartmouth-Hitchcock: “Thank you for this landmark article. The PDN patient population surely needs more treatment options and the HF-10 results in this study are quite impressive. Truthfully, I have not seen many of these patients during the year, but I imagine if you were to advertise to PCPs and endocrinologists, a substantial referral pattern would be established. That said, I still have my reservations. For one, safety is a major concern. There were no study-related AEs reported for the CMM group, while there were 18 AEs reported in 14 patients in the intervention group. Of the 90 participants that received implantation, five of them has issues with infection, wound dehiscence, and impaired healing. This is a high-risk surgical population with the average A1c of the included participants of 7.4% and an exclusion limit of 10%. We know from our recently reviewed NACC SCS guidelines that although consensus among surgical subspecialties has not been reached, "when considering hemoglobin A1c, a higher incidence of postoperative complications has been reported in patients with level > 7%, and the American Diabetes Association recommends levels <7% as an acceptable blood glucose target." I don't think this is a reason not to perform the procedure, but the treatment team must have a high suspicion for these potential complications during the follow-up process. Lastly, the lack of blinding is a major flaw of the study. The authors acknowledge that the potential placebo effects in the study may be significant. “

Jeff Krause, Fellow at Dartmouth-Hitchcock: “This was an interesting article that describes a unique treatment option for patients with diabetic peripheral neuropathy. As Lucas mentioned, one of the things that also caught my eye was the safety of the procedure versus the best available medical treatment. Though this procedure presents an increased risk over the medical treatment arm, the benefits seem to be drastic. There was a marked decrease in pain in HF-10 versus medical treatment and also some improvement in neurological functioning. There was improved sensation in a majority of HF-10 patients which may be beneficial in regard to foot ulcer identification and infection reduction. If discussing this treatment with a patient, it would be important to have a discussion of the risks and benefits of medical versus implant treatments. It is important to note, however, that the wound complication rate of 5.6% is consistent with the complication rate of SCS implants in populations without diabetes. I think an interesting investigation in the future would be the use of HF-10 versus lower frequency modalities. This article was sponsored by Nevro and a lot of the investigators received funding from this company. They mentioned that the paresthesia free modality would be better to prevent paresthesias, but I would prefer to see data than take their word for it. It will also be interesting to see if LDN will play a role for the medical management of DPN in the future.”

Zachary Carter, Fellow at Dartmouth-Hitchcock: “I am always a little wary about industry sponsored studies and this is a very big industry sponsored study. I think the things I found most interesting from this article include that neuropathic medications number needed to treat is 3.6-7.2 while the number needed to harm is 11.8-25.6. If the higher number needed to treat and the lower number of needed to harm were the exact number that is a very small therapeutic range. While the data does look very promising for high frequency in diabetic peripheral neuropathy it is comparing high frequency to medical management, not other SCS (even though the authors do elude to this in the discussion section when they discuss responder rates in other therapies/studies which I do not really feel they can make such comparisons as they are comparing apples to oranges when it comes to study designs outcomes patient populations etc). In addition, there were no adverse events for the CMM group while 6% of the patient had an adverse event during the 6th month trial. While this number does seem small, I do not think it is insignificant. In addition, they mention that two of the participants (about 2%) needed to have the implant removed within the six months. I would be interested to see what the long-term explant rate is at two years or even later.”