Safety and Efficacy of 10 kHz Spinal Cord Stimulation for the Treatment of Refractory Chronic Migraine: A Prospective Long-Term Open-Label Study

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ABSTRACT

Background: Refractory chronic migraine (rCM) is a highly disabling condition for which novel safe and effective treatments are needed. Safety and long-term efficacy of paresthesia-free high cervical 10 kHz spinal cord stimulation (SCS) were here prospectively evaluated for the treatment of rCM.

Materials and Methods: Twenty adults with rCM (mean numbers of preventive treatments failed: 12.2 ± 3.1) were enrolled in this single-center, open-label, prospective study and implanted with a 10 kHz SCS system (Senza™ system, Nevro Corp), with the distal tip of the lead(s) positioned epidurally at the C2 vertebral level. Safety and effectiveness outcomes, such as adverse events, headache and migraine reductions, responder rates, Migraine Disability Assessment (MIDAS), Headache Impact Test-6 (HIT-6), and Migraine-Specific Quality-of-Life (MSQ), were captured up to 52 weeks after implantation.

Results: Compared to baseline, at 52 weeks postimplantation, there was a significant reduction of mean monthly migraine days (MMD) by 9.3 days (\( p < 0.001 \)). Sixty percent and 50% of patients obtained respectively at least 30% and at least 50% reduction in mean MMD. By week 52, 50% of patients’ chronic pattern converted to an episodic pattern. The proportion of subjects classified with severe headache-related disability on the HIT-6, decreased from 100% to 60% at week 52. Meaningful improvements of headache-related quality of life measured by the MSQ scale were observed with mean gain of 24.9 ± 23.1 (\( p < 0.001 \)) points at 52 weeks. No unanticipated adverse device effects occurred. No patients required any additional device surgical revision.

Conclusion: 10 kHz SCS may be a safe and effective neurostimulation option for rCM patients. The paresthesia-free waveform constitutes an unprecedented advantage for future methodologically sound sham-controlled studies in headache neuromodulation.

Keywords: Chronic migraine, neuromodulation, refractory chronic migraine, spinal cord stimulation

Conflict of Interest: Adnan Al-Kaisy and Stefano Palmisani received funding for travel by Nevro Corp and Saluda and speaker honoraria from Nevro Corp. Samuel Wesley has received consultancy honoraria. Anand Rotte and Angela Santos are employees of Nevro Corp. Giorgio Lambru has received speaker honoraria, funding for travel, and has received honoraria for participation in advisory boards sponsored by Allergan, Novartis, Eli Lilly, and TEVA. He has received speaker honoraria and funding for travel from electroCore, Nevro Corp, and Autonomic Technologies. David Pang and Roy Carganillo have no conflicts of interest to disclose.

INTRODUCTION

Chronic migraine (CM) is considered a severe form of migraine affecting 1.4–2.2% of the general population with an annual incidence among episodic migraine (EM) people of 2.5%.\textsuperscript{1,2} Oral and injectable preventive treatments constitute the recommended management strategy for these patients. Integrating behavioral therapy with physical and pharmacological interventions has shown to be beneficial in some studies.\textsuperscript{3} The use of oral treatments leads to frequent tolerability issues and poor adherence whereas injectable treatments, including Onabotulinum toxin A (BoNT/A) and greater occipital nerve blocks (GONBs), seem to be beneficial in...
about half the patients. As a consequence, a significant minority of CM patients becomes refractory to treatments. Different definitions have been used over time to classify such difficult-to-treat CM patients, though largely speaking refractory CM (rCM) is diagnosed when patients with severe and disabling CM failed to respond/tolerate most of the established treatments used in migraine prevention. Newer injectable monoclonal antibodies that target calcitonin gene-related peptide have recently emerged as promising treatment options for patients with CM and rCM. However, given their recent emergence, long-term safety and efficacy is not yet established.

Occipital nerve stimulation (ONS) has been considered the treatment of choice for rCM for some time due to promising open-label evidence. However, when studied in randomized clinical trials, the benefits were less dramatic than hoped for. These trials have been criticized for methodological weaknesses, poor endpoint choice, unmitigated placebo effect, and a high rate of surgical complications, which may have obscured the full beneficial effect of ONS. Neurostimulation targeting the high cervical dorsal columns has emerged as a novel potentially feasible and safe treatment in rCM in open-label studies.

Spinal cord stimulation (SCS) at 10 kHz is a minimally invasive neurostimulation therapy that has shown promise as an intervention for patients with various chronic pain syndromes. Level I evidence for its efficacy in chronic back and leg pain was provided by a multicenter, randomized controlled trial (SENZA-RCT), pointing out its superior efficacy versus traditional SCS and added benefits such as the absence of paresthesia. These results were supported by several prospective and retrospective studies. Favorable results have also been reported in patients with neck pain, abdominal pain, peripheral polyneuropathies, and chronic widespread pain.

The precise mechanism of action of 10 kHz SCS has not yet been fully elucidated. Recent preclinical research suggested that pain sensory processing in the dorsal horn may be reduced by 10 kHz SCS at intensities below sensory thresholds due to activation of inhibitory interneurons in the dorsal horn. The research also observed that excitatory interneurons in the dorsal horn were not activated at this level of stimulation intensity. The latter finding suggests that 10 kHz SCS does not activate dorsal column fibers, which may account for the absence of paresthesia. The absence of paresthesia in 10 kHz SCS allows the patient to sleep and drive without having to turn the stimulation off.

The purpose of the present study was to assess the safety and long-term effectiveness of 10 kHz SCS delivered to the high-cervical spinal cord without a stimulation trial in a refined rCM population without medication overuse headache (MOH).

MATERIALS AND METHODS

Study Design and Selection Criteria

This was a prospective, single center, open-label study to assess the safety and efficacy of cervical 10 kHz SCS in the treatment of rCM. Eligible participants were adults aged 18–65 referred to the Headache Service, Guy’s and St Thomas Hospital, London, UK, who fulfilled the revised second version of the International Classification of Headache Disorders (ICHD-2R) diagnostic criteria for CM and who were refractory to medical treatments at the time of the screening. All participants were assessed by a board-certified headache neurologist (G.L.). An independent medical adviser confirmed that each subject met the eligibility criteria after enrolment.

Eligible participants had to fail to respond or tolerate at least three medications with established evidence in migraine prophylaxis one of which had to be topiramate, unless contraindicated, as well as failed BoNT/A administered as per PREEMPT protocol. Treatment failure was defined as treatment discontinuation due to unacceptable side effects and/or absence of reduction in headache frequency, duration, or severity after administration of a preventive medication for at least 12 weeks. For patients who underwent a trial with BoNT/A, failure to obtain at least 30% reduction in headache days after two sets of injections was considered treatment failure.

Table 1 summarizes the core inclusion and exclusion study criteria. Patients with MOH as per the International Headache Society (IHS) criteria were excluded. Patients on stable prophylaxis medication regime for at least two months prior to enrolment were allowed to enter the study. The screening process included reviewing existing cervical magnetic resonance imaging or obtaining new ones to confirm eligibility for SCS implant. Eligible subjects completed a 28-day migraine-specific headache diary designed by the investigators, which also served as their baseline for the study.

Ethics approval for the study was granted by North East - York Research Ethics Committee on May 26, 2015. Each enrolled patient provided informed consent. The study was registered with the International Standard Randomized Controlled Trial Number (ISRCTN) registry (ISRCTN94247798).

Surgical Procedure

Eligible subjects were implanted with a 10 kHz SCS system (Sensa™ system, Nevro Corp, Redwood City, CA) without undergoing a stimulation trial. The stimulation device was activated four weeks later. Subjects were subsequently assessed at 4, 8, 12, 24, and 52 weeks after device activation (Fig. 1a). Stable medication was maintained up to the 12-week visit. Thereafter, prophylactic medication could be optimized if necessary. Subjects were instructed not to change other concomitant medication. Device reprogramming was allowed at any visit after device activation if required.

The surgical procedure was carried out under general anesthesia in a single stage. A 14-gauge Tuohy needle was introduced to the epidural space at the upper thoracic level using the loss of resistance technique. In view of the lack of clear guidance on number of leads needed in high cervical SCS in migraine treatment, one or two percutaneous leads were used. One percutaneous lead was adopted for 17 subjects and two leads for three patients. Under fluoroscopic guidance, one or two leads were directed cranially toward the posterior epidural space and secured with the distal tip placed at the C2 vertebral level (Fig. 1b) targeting the trigemino-cervical complex (TCC). The lead(s) were secured by a suture to the supraspinal ligament/paravertebral muscle fascia. A tunneling tool was used to pass the lead to a subcutaneous pocket in the paraspinal region where the implantable pulse generator (IPG) device was subsequently placed and connected to the epidural lead(s). Intravenous antibiotics were administered perioperatively, followed by a three-day course of oral antibiotics at discharge.

Activation of the device was delayed for four weeks to allow wounds to heal and the perioperative analgesics to wash out. After
this period, stimulation location and device program settings to provide optimal headache relief were determined for each subject starting at the C2/C3 vertebral level (frequency: 10 kHz; pulse width: 30 μsec; amplitude: 0.6–4.0 mA).

### Table 1. Key Inclusion/Exclusion Criteria.

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<thead>
<tr>
<th>Inclusion criteria</th>
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<tr>
<td>18 years of age or older</td>
<td>PHQ-9 score of more than 19</td>
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<tr>
<td>Diagnosed with chronic migraine (CM) as per ICHD-2R criteria for at least six months</td>
<td>Contraindicated for cervical placement of SCS leads</td>
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<tr>
<td>Refractory to conventional pharmacological CM treatment (at least three prophylaxis therapies of which one is topiramate if not contraindicated)</td>
<td>Medical condition or pain in other area(s) that could interfere with study procedures and/or confound evaluation of study endpoints</td>
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<tr>
<td>Failed botulinum toxin type A treatment</td>
<td>Diagnosed untreated severe psychiatric disorder(s)</td>
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<td>Optimal and stable CM prophylaxis therapy for at least two months</td>
<td>Known history or suspicion of substance abuse or addiction</td>
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<tr>
<td>Developed CM before the age of 60</td>
<td>Existing drug pump and/or another active implantable device</td>
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<td>Appropriate candidate for cervical SCS</td>
<td>Noninvasive neuromodulation is being used or planned</td>
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<td></td>
<td>Previous exposure to any implantable neurostimulation device</td>
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<td></td>
<td>Alternative therapy to treat migraine is being used or planned</td>
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<td>Be pregnant or breastfeeding</td>
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### Figure 1. Subject disposition (a) and cervical lead placement (b).

**Outcomes**

Headache characteristics, including daily headache intensity, headache duration, presence of associated symptoms, and abortive treatment intake, were captured in the headache diary.
Subjects were asked to prospectively complete a headache diary for four weeks before each study visit. A “moderate or severe headache day” was defined as a day with headache lasting for ≥4 hours and with a severity of ≥4/10 on a verbal rating scale (0, no head pain, 10 worst pain ever experienced). A “migraine day” was defined according to the IHS classification criteria. A “headache-free day” was defined as a day without any head pain. Outcomes were collected at baseline and 4, 8, 12, 24, and 52 weeks after the device activation visit. The primary safety measure was the incidence of unanticipated adverse device effects (UADEs) at 12 weeks, though unanticipated device-related adverse events (AEs) and any other AEs were recorded at all follow-up times. A number of efficacy outcomes were evaluated at week 12 and during all other follow-up times, including: reduction from baseline in the number of moderate-to-severe headache days/month; reduction from baseline in the number of migraine days/month; proportions of participants achieving at least 30% and at least 50% response (ie, participants achieving ≥30% and ≥50% reduction in the monthly average number of migraine days during at weeks 12, 24, and 52); change from baseline in headache-related disability measured on the Migraine Disability Assessment (MIDAS) and Headache Impact Test (HIT-6) scales; change in headache-related quality of life (HRQoL) measured using the Migraine-Specific Quality-of-Life (MSQ) questionnaire. The MSQ instrument provided a total HRQoL score along with three subdomain scores: role function-restrictive (RR), role function-preventive (RP), and emotional function (EF). Additional efficacy outcomes included conversion from CM (≥15 headache days/month with ≥8 being migraine) to EM (<15 migraine days/month); impression of change in quality of life evaluated using the Global Impression of Change (GIC) questionnaires for patients and clinicians; and satisfaction with therapy. Speed of response was also analyzed. This was defined as the time needed for participants to reach the 30% response rate.

Statistics

Descriptive statistics were used to summarize baseline and outcome data collected, and statistical tests were used to determine significance of differences. Continuous variables were summarized using the number of observations, mean, standard deviation, minimum, median, and maximum. Two-tailed, Wilcoxon signed rank test, and paired samples t-test with a significance level of 5% were used. Categorical variables were summarized using frequencies and percentages. Reported follow-up times are relative to the device activation visit. Analyses were carried out in Microsoft Excel and IBM SPSS Statistics.

RESULTS

Demographics and Baseline Characteristics

Between September 2015 and October 2017, 74 subjects with rCM were prescreened for eligibility and 25 subjects were enrolled (Fig. 1a). Frequent reasons for exclusion at the prescreening phase were severe psychiatric disorders, incorrect diagnosis, CM patients not refractory, other headache disorders, or chronic pain disorders that would interfere with the study aim. All enrolled subjects were reviewed for eligibility by a medical adviser, resulting in two exclusions. Three subjects withdrew consent. The remaining 20 subjects underwent permanent implantation of a Senza™ SCS system (Neuro Corp, Redwood City, CA). All implanted subjects completed the scheduled study visits at 4, 8, 12, 24, and 52 weeks. The last study visit occurred in November 2018. The demographics and baseline characteristics of the implanted participants are detailed in Table 2. Mean age at implantation was 42.9 ± 10.5 years. Among the cohort, 85% were female. Subjects had suffered migraine for 19.2 ± 13.2 years, and CM for 10.1 ± 9.8 years. All subjects had severe migraine symptoms, were refractory to medical treatment, and baseline characteristics of the implanted participants are detailed in Table 2. Mean age at implantation was 42.9 ± 10.5 years. Among the cohort, 85% were female. Subjects had suffered migraine for 19.2 ± 13.2 years, and CM for 10.1 ± 9.8 years. All subjects had severe migraine symptoms, were refractory to medical treatments having failed a mean of 12.2 ± 3.1 preventive treatments (range 6–18) including topiramate, BoNT/A, and GONBs. The mean number of monthly headache days (MHD) and of monthly migraine days (MMD) at baseline were respectively 24.0 ± 5.0 and

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<th>Variable</th>
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<td>Gender</td>
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<tr>
<td>Male</td>
<td>3</td>
<td>42.9 ± 10.5</td>
<td>46 (24–59)</td>
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<tr>
<td>Female</td>
<td>17</td>
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<td>Age (years)</td>
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<tr>
<td>Weight (kg)</td>
<td>20</td>
<td>10.1 ± 9.8</td>
<td>6 (1–35)</td>
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<tr>
<td>Duration of migraine (years)</td>
<td>19*</td>
<td>22.5 ± 6.5</td>
<td>25 (7–28)</td>
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<tr>
<td>Duration of CM (years)</td>
<td>20</td>
<td>2.0 ± 5.0</td>
<td>26.5 (13–28)</td>
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<td>Baseline diary</td>
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<td>1.9 ± 3.8</td>
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<tr>
<td>Migraine days</td>
<td>20</td>
<td>3.4 ± 1.8</td>
<td>0 (0–28)</td>
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<tr>
<td>Headache days</td>
<td>20</td>
<td>8.1 ± 5.0</td>
<td>6 (3–24)</td>
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<tr>
<td>Headache free days</td>
<td>20</td>
<td>12.2 ± 3.1</td>
<td>12 (6–18)</td>
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<td>Number of botox treatments</td>
<td>20</td>
<td>128.7 ± 70.7</td>
<td>124 (17–260)</td>
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<td>67.1 ± 3.5</td>
<td>67.5 (62–74)</td>
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<td>Number of failed prophylactic treatments</td>
<td>20</td>
<td>33.4 ± 16.4</td>
<td>31.4 (6–60)</td>
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*One subject with unknown migraine start date.
22.5 (±6.5). Seventy-five percent of subjects reported a daily headache pattern at baseline with no headache-free days. All participants were classified in the severe impact category at baseline on both the HIT-6 and MIDAS scales (HIT-6 score: 60–78; MIDAS score: >20) (Table 2).

**Efficacy Outcomes**

Compared to baseline, the mean reduction in MHD at 12 weeks was 3.6 ± 7.2 days ($p = 0.039$), at week 24 was 2.8 ± 5.3 ($p = 0.021$), and at week 52 was 5.3 ± 7.4 days ($p = 0.004$). Compared to baseline, the mean reduction in MMD at 12 weeks was 6.7 ± 9.9 ($p = 0.007$), at week 24 was 5.0 ± 8.1 ($p = 0.011$), and at week 52 was 9.3 ± 9.3 days ($p < 0.001$) (Fig. 2a,b). At 52 weeks, the frequency of mean MHD decreased by 41%.

**Responder Rate**

Compared to baseline, the MHD responder rates (assuming a 30% or greater reduction in mean MHD) were 30%, 30%, and 50% at week 12, 24, and 52, respectively, whereas the MMD responder rates (assuming a 30% or greater reduction in mean MMD) were 45%, 35%, and 60% at week 12, 24, and 52, respectively (Fig. 2c). Compared to baseline, the MHD responder rates (assuming a 50% or greater reduction in mean MMD) were 15%, 5%, and 35% at week 12, 24, and 52, respectively, whereas the MMD responder rates (assuming a 50% or greater reduction in mean MMD) were 25%, 25%, and 50% at week 12, 24, and 52, respectively (Fig. 2d). At 52 weeks, 50% of patients displayed an EM pattern (Fig. 3).
Stimulation Location and Settings

The stimulation location and device program settings that provided the highest reduction in mean MHD during the 52-week follow-up period were recorded for each subject. In the whole cohort, the median number of programming visits required was 6 (range 1–8). For MHD responders, the median was 3 (range 1–8), whereas for nonresponders the median was 7 (range 5–8).

The best reduction in mean MHD was achieved in half of the cohort with stimulation located at the C3 vertebral level or C3/C4 disk level (Fig. 4a); in 60% of the cohort when using a simple bipole configuration (Fig. 4b) and in half of the cohort with a stimulation duty cycle (intermittent stimulation with rest in between pulses) between 50% and 100% (Fig. 4c).

HRQoL Outcomes

Headache-related disability improved throughout the study as measured by the MIDAS and HIT-6 scales. On both scales, all participants were classified as severely disabled at baseline. MIDAS score decreased from baseline by a mean of 41.7 ± 75.6 (p = 0.03), 47.1 ± 79.6 (p = 0.02), and 66.0 ± 80.7 (p = 0.006) points at 12, 24, and 52 weeks, respectively. The average MIDAS score for the cohort halved by 52 weeks. In addition, the proportion of subjects classified by MIDAS with severe headache-related disability decreased from 100% at baseline to 75% at week 52. HIT-6 score also reduced from baseline by a mean of 3.4 ± 5.1 (p = 0.008), 3.6 ± 5.7 (p = 0.011), and 5.9 ± 5.7 points (p < 0.001), respectively (Fig. 5a,b). On the HIT-6 scale, the proportion of subjects classified with severe headache-related disability decreased from 100% to 60% at week 52. Improved HRQoL, as measured by the MSQ scale, was also observed during follow-up, with mean gains of 13.7 ± 19.8 (p = 0.001), 16.2 ± 22.3 (p = 0.004), and 24.9 ± 23.1 (p < 0.001) points at 12, 24, and 52 weeks, respectively (Fig. 5c).

On the GIC questionnaires collected at 52 weeks, 75% of subjects were rated by their physician as “very much” or “much” improved

Figure 4. Highest monthly headache days reduction stimulation location (a), electrode configuration (b), and duty cycling (c). [Color figure can be viewed at www.neuromodulationjournal.org]
and 55% of subjects reported feeling “very much” or “much” improved (Fig. 6a,b). At the same visit, 70% of subjects were “very satisfied” or “satisfied” with their therapy, and 85% indicated that they would “highly recommend” or “recommend” their treatment.

Time Until Response
The time until onset of responder status is detailed in Figure 7. Among the ten subjects who achieved responder status during the 52-week follow-up period, four were responders by four weeks. Two further subjects achieved responder status between 8 and 12 weeks, and the remaining four subjects between 24 and 52 weeks. A similar trend over time was also observed among the 12 subjects who reported migraine response (≥30% reduction in migraine days/month).

Safety Outcomes
No UADEs were recorded at 12 weeks, or at any time during the study. By the final visit at 52 weeks, a total of 32 study-related AEs were recorded. Of these, 22 were classified as mild, eight as moderate, and two as severe. Nine of the 32 AEs were device-related, six were procedure-related, and 17 were stimulation-related. Of the nine device-related AEs, six were due to IPG site pain, and one was due to lead movement. Three cases of IPG site pain required device repositioning, and the single instance of lead movement was resolved with device reprogramming. All AEs were resolved, and no explants occurred.

DISCUSSION
All the study participants had long-standing CM symptoms and failed all the available, at the time of the study, preventive treatments, fulfilling the definition of medically refractory as per the updated European Headache Federation definition.7 This group of patients populates many of the headache clinics and inevitably constitutes a significant clinical challenge for headache specialists, which have no evidence-based treatment options to offer, leaving these patients with enormous levels of headache-related disability. The results of our study suggest that 10 kHz high cervical SCS may be a long-term effective treatment option for rCM. At one-year follow-up, the mean MMD frequency decreased by 9.3 days. Furthermore, 60% of subjects were considered responders to the treatment according to the IHS definition.38 Interestingly the majority of responders (50%) obtained a profound improvement, by reporting at least 50% reduction in mean MMD and in 50% of the participants, their long-standing chronic and often daily headache pattern reverted into an episodic pattern. The improvement of migraine symptoms in responders corresponded to a clinically meaningful improvement in headache-related disability and HRQoL scales.

10 kHz SCS has shown promise as an intervention for patients with various chronic pain syndromes.22 The feasibility of using the high cervical spine target in migraine has been confirmed in small retrospective studies and in one prospective study conducted in rCM with MOH. A retrospective study of low-frequency, high-cervical SCS in 17 rCM patients found a 50% response rate in 71% of patients at 15 months follow-up. Device-related complications were rare.19 After 25 months of follow-up, a retrospective study of high-cervical 10 kHz SCS conducted in a small series of refractory primary headache disorders showed a reduction of ≥50% in headache and migraine frequency in all rCM patients. Two of the seven patients required surgical revision, one due to lead migration and the other due to lead breakage.21 In a prospective case series of 14 rCM with MOH implanted with high-cervical 10 kHz SCS, 50% and 36% of subjects experienced respective reductions in headache frequency of >30% and >50% at six months follow-up. Headache-related disability scores also improved significantly. Only one patient required surgical revision.20 Our data confirmed these
promising results but in a carefully selected, diagnostically refined and prospectively studied population.

Our efficacy results in a highly intractable population are comparable to the outcomes of the ONS RCTs in CM.17,18 However, there are important differences in methodological aspects between this study and the ONS RCTs that may suggest superiority of high cervical HF10 SCS. First, participants selected for ONS had to have occipital pain or pain mainly originating from the occipital region, which implies that of the whole migraine population, participants were selected only among the 40% of those with predominantly occipital pain,17 limiting the generalization of the results to the whole migraine population. Our study did not select participants based on the head pain location. Second, a stimulation trial was used as a selection criterion especially in the pivotal ONS RCT.18 However, delayed clinical response to ONS in migraine has been shown, suggesting that basing patient’s selection upon a short stimulation trial may prevent a proportion of patients to experience the full benefit of the therapy. Indeed, in a large open-label prospective ONS study in rCM, the median time to effect in responders was four months,10 supporting this hypothesis. There is sparse literature on the ability of a percutaneous trial to predict long-term benefit of ONS in headache patients.14 Subgroup analysis of data from the PRISM study reported that a favorable response to a percutaneous treatment trial was moderately predictive of a 12-

Figure 6. Clinician global impression of change (CGIC) (a), patient global impression of change (PGIC) (b), patient satisfaction (c), and therapy recommendation (d). [Color figure can be viewed at www.neuromodulationjournal.org]

Figure 7. Time until onset of responder status. [Color figure can be viewed at www.neuromodulationjournal.org]
week response.\textsuperscript{39} Moreover, it is arguable that longer periods of stimulation in those who failed the trial might have resulted in benefit in the longer term, given that ONS usually induces improvements over weeks or months.\textsuperscript{40,41} Given the very little reported use of 10 kHz SCS for CM, it was assumed that a trial would not be predictive of long-term outcomes. The use of monthly headache diaries to assess response would also make assessing a short trial very difficult. Third, the population studied in the ONS RCTs had CM and not rCM. Their cutoff in terms of number of classes of preventive treatments failed was two and it was unclear how many classes or treatments the RCTs participants failed and if the study group was BoNTA nonresponders. This population seems to lack of the refractoriness clinical element, which, although not formally demonstrated yet, may require the lack of response to the established treatments at the point when a study is conducted. In our study, the mean number of treatments failed was 12 including topiramate, BoNTA, GONBs, and the other established classes of treatments used in migraine prevention. In the ONS literature, when a similar rCM population (mean of 9.36 treatments failed at baseline) was studied, the 30% responders at last follow-up was 34% compared to the 60% in our study, suggesting a more meaningful long-term effect of the HF10 SCS compared to ONS.

SCS has been sparsely tried in the treatment of headache disorders mainly because of serious concerns about its high device-related complications rate shown in some small studies.\textsuperscript{42,43} The use of ONS has been considered as less invasive than cervical SCS for refractory patients.\textsuperscript{44} It became subsequently apparent in the one-year open-label extension of the pivotal ONS RCT study, that the rate of device-related complications is concerning high and that 40.7% of the study participants required surgical re-intervention and 8.6% required hospitalization.\textsuperscript{45} Over a ten year period, lead migration was the most common complication reported on the MAUDE database for ONS implants at 16.7%, which has been supported in recent reviews.\textsuperscript{46–49} Our study found high cervical HF-10 SCS therapy to be safe and well tolerated with no UAEDs during the 52-week follow-up, in particular no lead migration that required a surgical reintervention. After 52 weeks, the majority of our 32 study-related AEs were mild or moderate in severity (94%). All AEs were resolved, and no explants occurred. Notably, our incidence of lead migration was only 3.1% relative to all AEs. The single case was resolved with device reprogramming. It may be possible that leads placed in the occipital subcutaneous tissue may be more vulnerable to dislodgement due to frequent flexion, extension, and rotation of the neck and head, whereas epidural axial leads placements guarantee better stability, hence the lower lead migration rate compared with ONS. It also likely that in large specialist centers with years of experience in invasive neuromodulation, the rate of device-related complications is low.\textsuperscript{1,26}

HF10 SCS has been shown to inhibit evoked afferent nociceptive inputs by modulating wide-dynamic range neuronal activity in the spinal cord of different animal models.\textsuperscript{50} We postulated that application of this therapy at the epidural level of the dorsal columns of the high cervical spine may modulate TCC fibers and in turn improve migraine symptoms. Our study also allowed some interesting clinical observations that may shed more light on the mechanisms of action of HF10 SCS in migraine, including the time until onset of response as well as the stimulation location that provided optimal headache relief in each subject. Studies of ONS in various headache syndromes (including CM) have reported a delayed treatment effect in some patients, usually several months.\textsuperscript{10,40,51,52} In our study, 40% of responders achieved responder status by four weeks, and a notable increase in this proportion was observed between 8 and 12 weeks. This may indicate an earlier response compared to ONS in CM patients, but this requires further investigation in a larger population. It was also interesting to note in our study that half of the cohort achieved their best reduction in monthly headache/migraine days with stimulation located at the C3 vertebral level and the C3/C4 disk level. Since the TCC is thought to play an important role in the pathogenesis of migraine,\textsuperscript{53} it has been suggested that modulation of the TCC via stimulation of the dorsal column at the C2/C3 level may provide a therapeutic effect in primary headache.\textsuperscript{51} Our results suggest that stimulation at other cervical vertebral levels may also be effective.

The main limitations of this study are the lack of a randomized control group and small sample size. Consequently, our results should be interpreted with caution, although it is unlikely that the positive results are only due to a placebo effect, given that recent clinical trials have shown how in treatment-resistant migraine patients the placebo effect is significantly low compared to naïve to treatment migraine patients (FOCUS\textsuperscript{54} and CONQUER\textsuperscript{55} studies). The foremost strength of this study is the inclusion of a highly intractable population with a significant unmet need for novel treatments. Additional strengths include the prospective nature of the data collection as well as follow-up of all implanted subjects through to the end of the study.

CONCLUSION

High-cervical 10 kHz SCS could constitute an emerging treatment modality for patients with rCM. The results of our prospective study suggest that the therapy may be a safe, effective, and well-tolerated preventative treatment. The ultimate goal of migraine treatments is to restore patients function and improve headache-related QoL. At one-year follow-up, the improvement in headache outcomes led responders to experience a significant and clinically meaningful improvement in MIDAS, HIT-6 scores, and MSQ. The patient and clinician GIC outcomes further reflect this meaningful improvement in quality of life, supporting the need of exploring this treatment in large RCT. Given the lack of paresthesia, a feasible sham could be created and compared to 10 kHz SCS enabling to conduct the first ever invasive neuromodulation RCT in primary headache disorders to establish the role of 10 kHz SCS in the management of rCM.

Acknowledgement

The authors sincerely thank the patients and their families for participating in this study.

Authorship Statements

Dr Al-Kaisy, Dr Lambrou, Dr Palmisani, and Dr Pang contributed to study design and patient recruitment; Dr Lambrou contributed to migraine diary design, patients’ screening, selection, and follow-up. Dr Al-Kaisy, Dr Lambrou, Dr Palmisani, Drs Pang, Samuel Wesley, Roy
Carranillo, and Angela Santos contributed to patient follow-up and data collection. Dr. Al-Kaisy, Dr. Lambru, Dr. Palmisani, Drs. Pang, Samuel Wesley, Angela Santos, and Anand Rotte provided input on the interpretation of the data analysis, and manuscript drafting and revision. Nevro Corp has provided funding for the study, statistical support, and data analysis with input from all the authors. All authors approved the final manuscript.

How to Cite This Article:

REFERENCES
This is a fine study of high cervical SCS for the treatment of migraine, yielding impressive results. The first description of high cervical SCS for the treatment of headache syndromes dates back more than 10 years (Wolter T, Kaube H, Mohadjer M. High cervical epidural neurostimulation for cluster headache: case report and review of the literature. Cephalalgia. 2008;28:1091–1094). While the first studies focused on conventional SCS in cluster headache (Wolter T, Kiemen A, Kaube H. High cervical spinal cord stimulation for chronic cluster headache. Cephalalgia. 2011;31:1170–1180) and in migraine (De Agostino R, Federspiel B, Cesnulis E, Sandor PS. High-cervical spinal cord stimulation for medically intractable chronic migraine. Neuromodulation. 2015;18:289–296; discussion 296), this study is the third examining hSCS. (Arcioni R, Palmisani S, Mercieri M, et al. Cervical 10 kHz spinal cord stimulation in the management of chronic, medically refractory migraine: a prospective, open-label, exploratory study. Eur J Pain. 2016;20:70–78) (Lambru G, Trimble M, Palmisani S, Smith T, Al-Kaisy A. Safety and efficacy of cervical 10 kHz spinal cord stimulation in chronic refractory primary headaches: a retrospective case series. J Headache Pain. 2016;17:66). It is quite commendable to advance this treatment option further, but it remains unclear, whether hSCS is more effective than conventional SCS in the treatment of primary headache disorders. To this end, a randomized controlled study would have to be conducted. While blinding is possible in hSCS, it is not in conventional spinal cord stimulation. However, still an unblinded controlled study would be conceivable. Also, further stimulation paradigms such as burst stimulation should be examined.

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[Correction added on July 6, 2021 after first online publication: The name of the author of the Comment above has been corrected.]

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The use of neuromodulation for treatment of severe headaches has been a subject of many investigations, and the jury is still out on whether one stimulation target or particular paradigm is more effective than others. Over the years, both invasive and non-invasive modalities have been used, and several approaches including transcervical supraorbital stimulation and peripheral nerve stimulation of the occipital nerves have received regulatory approvals in multiple geographic regions.

The authors of this study reached a remarkable degree of improvement in most refractory patients with chronic migraines with the use of paresthesia-free high frequency stimulation of the cervical spinal cord based on 20-patient cohort. This finding is very encouraging and deserves to be used as a rationale for a larger, multicenter controlled prospective study, that, hopefully, will be more convincing than earlier similar studies of occipital nerve stimulation.

Ultimately, however, one will have to decide if each individual patient with chronic migraines can be treated with the same stimulation modality or if there is a need in an individually-tailored algorithm that would be based on some physiological markers or pain patterns with escalating degree of invasiveness designed to compensate for incomplete relief or treatment failure. For this, I can envision a randomized comparative study of different modalities that would allow us to gauge safety, feasibility and cost against effectiveness and longevity of effect.

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