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Kinetic oscillation stimulation for the preventive treatment of refractory chronic migraine: a case series

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ABSTRACT

Background: Refractory migraine refers to a subtype of chronic migraine in which individuals experience severe and disabling attacks that do not respond adequately to any pharmacological treatment. In recent years, neuromodulation techniques have emerged as promising therapeutic avenues for refractory migraine management.

Methods: Four patients with refractory chronic migraine were offered a six-week cycle of kinetic oscillation stimulation (KOS), a novel approach of neuromodulation whose target is the sphenopalatine ganglion (SPG). Migraine frequency and medication usage were recorded in a diary; intensity of pain and impact of migraine on patient's behavior were assessed with validated clinical scales.

Results: All except one patient completed the scheduled sessions. Severity of pain and drug consumption remained stable in most cases. After one month of active stimulation, migraine frequency did not differ substantially from pre-operative monthly average, except in one subject who recorded a reduction of 11 monthly migraine days (MMD). A second treatment cycle was proposed for this patient, considering the excellent clinical outcome.

Conclusions: KOS could be a helpful resource and drug-sparing option for selected patients with refractory migraine. However, more evidence is needed to confirm its efficacy and establish a shared usage protocol.

Key words: refractory migraine, kinetic oscillation stimulation, neuromodulation.

Introduction

Refractory migraine refers to a challenging condition where headaches do not improve despite extensive treatment efforts, often leading to significant disability and reduced quality of life.

According to the European Headache Federation (EHF), refractory migraine is defined by the failure of all available preventative treatments with at least 8 debilitating headache days per month for a minimum of 6 consecutive months.(1)

For the patient dealing with chronic pain, ongoing disability, and uncertain treatment outcomes can worsen emotional distress and migraine symptoms. In such cases, it is crucial to explore alternative strategies.

Neuromodulation is gaining ground as a valuable strategy, especially for medically complex patients who, having found conventional therapies to be ineffective, seek non-medication alternatives.(2)

Treating migraine with sphenopalatine ganglion (SPG) neuromodulation has shown promising results, with some studies demonstrating significant reduction in frequency, severity, and duration of attacks. The SPG is believed to play a pivotal role in headache pain and cranial autonomic symptoms as a result of activation of the trigeminal-autonomic reflex (TAR).(3) Given its significance in initiating and sustaining pain, the SPG has been proposed as a target for both acute and preventive treatment of migraine.

The TAR is a complex pathway involving the trigeminal nerve, brainstem structures like the trigeminal cervical complex (TCC), and parasympathetic components originating from the superior salivatory nucleus (SSN) and projecting through the SPG.(3) This pathway has been implicated in migraine pathophysiology, particularly in the modulation of vascular and inflammatory responses. The SPG, easily accessible through the nasal mucosa, is a key player in this reflex pathway.(4)

Kinetic Oscillating Stimulation (KOS) with the Chordate S211 system is a non-invasive technique designed to apply low-frequency mechanical vibrations to the nasal cavity, which is believed to exert beneficial effects on the autonomic nervous system (ANS). It was originally devised to offer a painless and efficient solution for chronic rhinitis.(5) The KOS device consists of a controller unit connected to a disposable catheter via a flexible plastic tube, which provides oscillatory stimulation to the nasal mucosa. The catheter, pre-lubricated with paraffin gel, is inserted into each nostril. The catheter tip is inflated and subjected to oscillatory motion for 10 minutes at a pressure of 95 mbar and a frequency of 68 Hz (**Figure 1**).

Application in the field of migraine stems from the results of a randomized controlled study where patients receiving active stimulation with KOS in the acute phase of a migraine attack reported a significant reduction in average pain score compared to placebo, with sustained results at 2 and 24 hours after treatment.(6)

In a subgroup analysis of a larger randomized clinical trial designed to explore the clinical efficacy of KOS in the preventive treatment of chronic migraine, the active intervention resulted in a decrease of monthly migraine days (MMD) from the initial assessment to weeks 3-6 of therapy and follow-up time in contrast to sham stimulation.(7) Drawing from this evidence, KOS obtained CE authorization with specific indications for chronic migraine in adults.

In light of the above, we have proposed this novel form of neuromodulation to some of our patients suffering from refractory migraine.

Case Series

Among the patients followed at our Headache Center of the

Fondazione Policlinico Campus Bio-Medico in Rome, we identified subjects who had already tried multiple therapies, including monoclonal antibodies targeting the calcitonin gene-related peptide (CGRP) pathway, with limited success.

From the clinical records of patients treated with anti-CGRP monoclonal antibodies, we selected 4 subjects who fulfilled criteria for chronic refractory migraine. After a complete clinical evaluation, we collected informed consent and offered them a six-week treatment with KOS as an additional therapy, adopting the protocol outlined in the study.(7)

Each session of stimulation was scheduled to last 10 minutes in each nasal cavity, for a total of 20 minutes per treatment. Only relevant abnormalities in the nasal cavity or recent surgery in the facial region constitute contraindication to KOS treatment, but none of the enrolled subjects had these conditions. A stable prophylactic medication regimen was admitted, as well as the use of symptomatic medications for pain control.

Patients were requested to keep a diary to record headache and migraine days, any changes in their health status, and concomitant medications they might have used.

Prior to each stimulation, each patient was asked to complete a questionnaire containing validated clinical scales (BS-11, PPI, BRS-6, SF-MPQ, HADS) to assess any benefit occurring the week preceding the ongoing session. Specifically, we employed the 11-point Box (BS-11) scale and the Present Pain Intensity (PPI) scale to evaluate pain severity during migraine episodes. To inspect the functional impact and emotional dimensions of pain, we utilized the 6-point Behavioral Rating (BRS-6) Scale and the Short-Form McGill Pain Questionnaire (SF-MPQ). Additionally, the Hospital Anxiety and Depression Scale (HADS) was used to screen for symptoms of anxiety and depression in a clinical setting.

Case 1. A 70-year-old woman has been followed by our center since 2015. Her medical history was positive for arterial hypertension, dyslipidemia, and depressive disorder. She has suffered from chronic migraine and episodic tension-type headaches for at least thirty years.

Despite an extensive course of medical management, which included all approved conventional therapies, the problem progressed to the point of complete disability with daily attacks and regular overuse of symptomatic medications. She failed a trial with monoclonal antibodies (erenumab) and Onabotulinumtoxin-A, mildly impactful only at the outset and for a few months. She also explored non-pharmacological therapies, supplementing drugs with dietary changes (ketogenic diet) and psychotherapy. Ultimately, she was enrolled in a clinical trial with atogepant but discontinued shortly after for lack of efficacy. Her pain is now unilateral and throbbing, with a reported frequency of 28 MMD, heavily impairing her function and quality of life.

Case 2. A 64-year-old woman who has been affected by chronic migraine for at least 10 years. She also suffers from hypertension, hypothyroidism, and paroxysmal atrial fibrillation. Her past medical history included arthroscopic knee surgery to treat osteoarthritis and abdominal surgery for body contouring. More recently, she developed a major depressive disorder as a coexisting condition. Since 2017, she has been followed by our center, where she was offered numerous treatments for migraine prevention, such as sodium valproate, topiramate, propranolol, and amitriptyline. Triptans were effective for acute pain, but poorly tolerated. She has been treated with Onabotulinumtoxin-A for four quarters, but she dropped out due to reduced efficacy. She started fremanezumab with monthly administration, but she quit shortly after due to poor satisfaction. Since 2023 onwards, she has been experiencing daily attacks with bilateral excruciating pain to the point where she has lost confidence in conventional medications and has expressed a preference for a non-pharmacological approach.

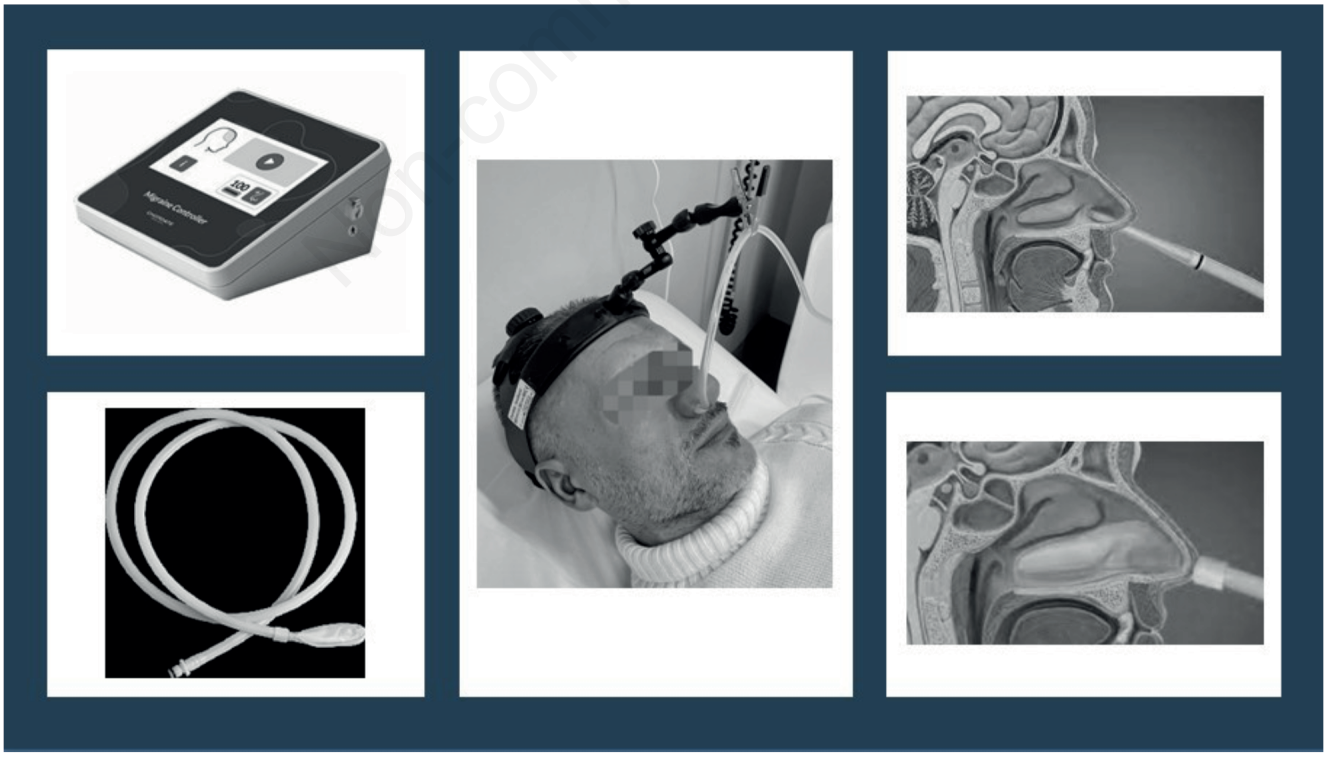

Figure 1. An explanatory image illustrating the functioning of KOS (Chordate System).

Case 3. A 72-year-old male has been followed by our center since 2013. His past medical history covers a long psychiatric follow-up for neurotic depression with associated sleep disorders, such as insomnia and sleep apnea. His comorbidities are arterial hypertension and essential tremors. In 2018, he was diagnosed with chronic migraine and associated medication overuse. Several classes of antidepressants have been employed as first strategy, but the outcome has been erratic and often inconsistent. He tried all the approved conventional therapies, even those of second choice, and not supported by strong evidence. His response to Onabotulinumtoxin-A was variable, with partial benefit observed intermittently and not consistently every month. Finally, he did not respond to anti-CGRP medication (fremanezumab), which was responsible for the worsening of the condition. In the last two years, migraine has been characterized by mild to moderate pressing pain, with few autonomic symptoms, alternating sides, and attacks of longer duration and early recurrence.

Case 4. A 60-year-old man with a long history of migraine since childhood and no meaningful medical history. His migraine attacks are characterized by unilateral pain in the frontotemporal region, with pulsating quality and moderate to severe intensity. He also reports cranial autonomic symptoms, primarily mild tearing on the side of pain.

Despite having tried several preventive drugs, he only experienced temporary improvement. He also suffered from medication overuse headaches, requiring multiple detoxification cycles. Other interventions, such as C2 dorsal root ganglion radiofrequency ablation and Onabotulinumtoxin-A injections, did not lead to significant amelioration.

He was later diagnosed with hypertension and treated with candesartan for potential benefits on migraine. Additionally, he tried erenumab which yielded modest results but did not sustainably reduce migraine frequency.

Despite various interventions, his migraine frequency remains high, with an average of 18 MMD.

Results

Patient demographics and characteristics are illustrated in **Table 1**. The median age was 64 years (range 60-72), and the median migraine duration was 30 years (range 20-45). At baseline evaluation, all patients fulfilled the criteria for refractory migraine (1), and three out of four subjects also met criteria for medication overuse headache (MOH).(8) All except one subject had unilateral attacks featuring elements of both sharp and constant pain. Only one patient reported autonomic symptoms. Additionally, two patients were co-diagnosed with other chronic pain syndromes, also complaining of poor quality of sleep. Two patients were managing their attacks with non-steroidal anti-inflammatory drugs (NSAIDs), one patient with triptans, and another with both types of medications.

The baseline disability scales reported quite elevated mean scores (68 at MIDAS and 67 at HIT-6). On self-reporting scales, pain intensity was medium-high (an average score of 8 at BS-11), as was the impact of pain on patient behavior (a median of 4 at BRS-6) (**Table 2**). Only one patient exhibited scores suggestive of severe depression at the self-assessment with HADS.

Active treatment was well tolerated by all subjects, with only negligible discomfort caused by inserting the stimulation catheter into the nostrils. All patients underwent active treatment in the interictal phase, or at most in the prodromal or postdromal phase of a migraine attack, with no particular relief or exacerbation of perceived pain at the end of active stimulation.

Table 1. Case series demographics and clinical characteristics.

Pts	Sex	Age	Migraine duration (yrs)[a]	Pain localization	CASs	Preventatives failed[§]	Acute treatment	Analgesic overuse	Other CPS	Sleep disturbances
1	F	70	30	Unilateral	No	All classes	NSAIDs	Yes	Yes	Yes
2	F	64	20	Bilateral	No	All classes	NSAIDs, triptans	Yes	Yes	Yes
3	M	72	45	Unilateral, alternating side	No	All classes	triptans	Yes	No	No
4	M	61	35	Unilateral	Yes[†]	All classes	NSAIDs	Yes	No	No

CASs, cranial autonomic symptoms; CPS, chronic pain syndromes; [a]From episodic, not from chronification; [§]including anti-CGRP mAbs; [†]lacrimation on the side of pain.

Table 2. Summary of migraine-related disability scores and clinical outcomes at T0 (baseline), T4 (1 month of active stimulation) and T6 (end of stimulation cycle).

Pts		MMDa	MMI[a]	HIT-6[a]	MIDAS[§]	HADS-A	HADS-D	BS-11	PPI	BRS-6	SF-MPQ
1	T0	26	24	72	80	20	15	9	5	5	32
	T4	21	22	76		21	16	10	5	5	38
	T6										
2	T0	28	30	67	53	5	6	8	3	4	23
	T4	24	24	60		5	7	7	3	4	20
	T6					7	8	7	3	4	22
3	T0	28	35	64	76	8	10	9	4	3	15
	T4	22	29	61		7	12	8	3	4	15
	T6					9	10	9	4	4	18
4	T0	18	16	65	63	3	1	6	3	4	12
	T4	7	9	46		1	1	4	2	3	8
	T6					1	0	3	2	2	5

T6 for Pt 1 is not available due to drop out at T4; unless otherwise specified, all items refer to the prior week (time period between two sessions or for T0 standard week); [a]with reference to the 1 month prior; [§]with reference to 3 months prior; MMD, monthly migraine days; MMI, monthly medication intake; HIT-6, Headache Impact Test; MIDAS, migraine disability assessment; HADS-A, hospital anxiety and depression scale - anxiety; HADS-D, hospital anxiety and depression scale - depression; BS-11, 11-point box scale; PPI, present pain intensity; BRS-6, 6-point behavioral rating scale; SF-MPQ, short-form McGill pain questionnaire.

Three patients completed all six stimulation sessions, whereas one patient dropped out at T4 due to substantial worsening of headache. All except one patient experienced a halving of weekly attacks at T2, but such a trend was no longer observed at the successive time points. The tendency to treat acute pain remained comparable to the baseline for each patient, with the number of self-administered symptomatic treatments per week closely related to the number of attacks. Patient-reported outcome measures did not reveal notable differences between T0 and T6, except in one patient where the pain descriptors initially ranking maximal in all items changed from mild to moderate in the greater part of indicators. In this specific patient we observed a remarkable lowering in terms of frequency with 11 fewer MMD recorded in a month of active treatment compared to when not in therapy. Hence, given the significant clinical achievements obtained during and immediately after the first cycle, we offered the patient another round with KOS one month after discontinuation.(9)

Discussion

Kinetic oscillation stimulation works by delivering mechanical vibrations to targeted areas of the nasal mucosa, operating in close proximity to SPG endings.(6) While the exact mechanism of action remains to be fully understood, it is argued that KOS may act by stabilizing autonomous imbalance, regulating cranial parasympathetic outflow, and potentially depleting stored neurotransmitters involved in the dilation of the cerebral vasculature.(10)

In recent years, a deeper understanding of the mechanisms underlying the pathophysiology of migraine has been achieved, and promising therapeutic strategies are emerging.(11) Despite this, some patients are still difficult to treat because they do not respond adequately to conventional or innovative therapy, neither used alone nor in combination with other treatments. The frustration generated by the limited treatment options encounters the need for healthcare providers to offer new alternatives with solid scientific bases. In this scenario, neuromodulation becomes attractive for several reasons: first, because it is a non-pharmacological approach, which some patients may prefer after prolonged and ineffective use of medications; second, for its safety profile and wide range of applicability.

Nonetheless, the findings in our small population do not align with those highlighted in previous studies.(8) With the exception of a single case where the outcome measures were decidedly positive, in the other patients no significant differences were observed from pre- to post-treatment.

The responder profile is that of a middle-aged male with unilateral pulsating pain, suboptimally responding to symptomatic treatments and with present, albeit mild, autonomic symptoms. His baseline HADS (both in anxiety and depression subscales) and BS-11 scores were the lowest among all subjects and further improved over the sessions. Although he had been a heavy abuser in the past, at the time of enrollment, while still meeting the criteria for MOH, his monthly consumption of symptomatic treatments was notably lower than one of the other patients (16 MMI compared to an average of 26 MMI).

It is challenging to posit the potential reasons behind such an uneven response to treatment among our patients.

What can be hypothesized is that the presence of autonomic symptoms may indicate a minimal, but still valid, sensitivity of the trigeminal structures to external stimuli, where the strategy of pain alleviation with sensory modulation is still viable. Structural alterations in the TCC, often associated with central sensitization, may disrupt functional feedback regulation between the trigeminal nucleus caudalis (TNC) and ANS.

Additionally, psychopathological profiles may have played a role in non-responders, as the efficacy of intervention correlates inversely with the severity of depression.

Another factor that could account for the recorded differences may be medication intake, which was significant in all patients but considerably lower in the sole responder.

Our study has several limitations. First, it is a small case series; thus, caution is needed in exposition and interpretation of the data. Additionally, there is no control group or validated sham procedure to compare the findings, and results on long-term treatment are available only for one patient out of the four considered in the study.

Conclusively, our findings provide only preliminary information on KOS as a potential treatment in refractory migraine. Given the unpredictable nature of migraine and the unsuitability of applying stimulation in a non-domestic setting, KOS does not appear to be a practical solution for the treatment of acute attacks.

Nonetheless, due to its safety and low invasiveness, it may be a suitable option for supplementary treatment in notably resistant and refractory cases.

Conclusions

This small series provides additional evidence of how KOS could be a safe and well-tolerated option in difficult-to-treat patients. The efficacy observed in one of the four subjects was so dramatic that it led us to suggest a second round of stimulation, extending the duration of active treatment beyond any previous attempt. However, due to the limited number of patients, it is not possible to adjust for potential confounding. A larger cohort is required to validate our findings and confirm the utility of KOS in the subset of refractory chronic migraineurs.

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