Non-invasive Vagus Nerve Stimulation (nVNS) for the Acute Treatment of Migraine Without Aura in Adolescents: Preliminary Clinical Experience

Licia Grazzi, MD[1]; Eric Liebler[2]; Gabriella Egeo, MD, PhD[3]; Piero Barbanti, MD, PhD[3]

[1]Headache Center, Carlo Besta Neurological Institute and Foundation, Milan, Italy; [2]electroCore, LLC, Basking Ridge, New Jersey, USA;
[3]Headache and Pain Unit, Department of Neurological Motor and Sensorial Science, Istituto di Ricovero e Cura a Carattere Scientifico, San Raffaele Pisana, Rome, Italy

Introduction

Migraine Without Aura in Adolescents

- Adolescents represent a sensitive patient population, with a migraine prevalence ranging from 6% to 20%[1]
- Among adolescents, females are more commonly affected than males, and migraine without aura is more frequent than migraine with aura[2,3]
- Diagnosis is challenging because of the variation in presenting symptoms over the course of childhood and the lack of formal characterisation by *International Classification of Headache Disorders, 3rd edition (beta version) (ICHD-III beta)* criteria[4,5]
- Compared with the adult population, adolescents are known to experience a faster onset and shorter duration of attacks, sometimes lasting only 1 hour[4-6]
- Short attack durations may limit the time available to seek and achieve pain relief from acute pharmacologic therapies, which appear to have minimal effects in clinical studies of adolescents[1]
  - Other potential explanations for this apparent treatment refractoriness include differences in migraine pathophysiology and in the time required to achieve maximum plasma concentrations between adolescents and adults
- The sensitivity and unique challenges of adolescent migraine have contributed to a paucity of large rigorous studies, limiting our understanding of this population and its treatment[2,4,6,7]

Current Acute Treatments for Adolescents With Migraine

- Oral nonsteroidal anti-inflammatory drugs and nasal triptans appear to be effective in paediatric migraine,[6-8] but only 2 nasal triptans (sumatriptan and zolmitriptan) and 2 oral triptans (almotriptan and rizatriptan) are approved by the EMEA and FDA, respectively, for the acute treatment of adolescent migraine[1,2]
- Use of these agents may be hindered by a late onset of effects given the short course of migraines in this population and by parental resistance to drugs and the associated potential risks of adverse events and medication overuse[2,6]

Non-invasive Vagus Nerve Stimulation

- Non-invasive vagus nerve stimulation (nVNS; gammaCore®) is a novel neuromodulation technique (Figure 1) that has demonstrated safety, tolerability, and efficacy in recent clinical studies of the acute and prophylactic treatment of migraine[9-12]
- The practicality and favourable risk-benefit profile of nVNS make it appealing for adolescents with migraine, who are avid users of handheld devices[13] and are particularly in need of treatments that exert fast effects without drug-related concerns and adverse events[2,6]

Figure 1. Non-invasive Vagus Nerve Stimulation Device

Image provided courtesy of electroCore, LLC.

Aim

- The objective of this case series was to assess preliminary experience with nVNS as a potentially safe, well-tolerated, and effective acute treatment option for adolescents with migraine without aura

Methods

Case Series

- This open-label pilot assessment comprised a single 1-month period, during which adolescents from the Headache Centre's outpatient service at the Carlo Besta Neurological Institute and Foundation received acute nVNS treatment for their migraine attacks
- Parents provided informed consent for their child's participation, often on the basis of a family history of migraine and experience with nVNS treatment

Patients

- All patients were
  - 13 to 18 years of age
  - Diagnosed with migraine without aura according to *ICHD-III beta* criteria
  - Experiencing a frequency of migraine attacks of 5-8 d/mo, as recorded retrospectively at the beginning of the assessment period
  - Not receiving prophylactic medications for migraine

Intervention

- The nVNS device (Figure 1) is applied transcutaneously and produces a proprietary low-voltage electrical signal that is transferred to the cervical branch of the vagus nerve
- Patients received acute nVNS treatment for at least 4 to 8 migraine attacks over the course of 1 month
- Acute treatment for each attack was administered on the right side of the neck as a single 2-minute stimulation followed by a second stimulation, if needed, within 1 hour

Device Training

- Patients participated in small-group training sessions at the centre with their parents, a neurologist, and a nurse counsellor
- During these sessions, basic information on vagus nerve physiology, migraine pathophysiology, and the neurostimulation process was provided, and an animated educational movie on the possible mechanism of nVNS was shown
- All participants applied the new information in a practical hands-on demonstration to ensure treatment adherence for optimal effectiveness

Headache Diaries and Patient Interview

- Headache diaries were used to track the patients' headache days, pain intensity, and rescue medication use
- At 60 minutes and 24 hours after the treatment of each attack, patients were asked to rate pain intensity from 0 to 10 using a visual analogue scale (VAS), with higher scores indicating greater pain
- Information on safety, tolerability, and device perceptions was captured in an in-person interview with patients and their parents at the end of the 1-month assessment period

Outcomes

- Successfully treated attacks
  - Defined as treated attacks that became pain-free or mild within 1 hour after nVNS treatment
  - Acute rescue medication use within 2 hours was considered a treatment failure
- Reduction in mean VAS score at 1 hour
- Safety and tolerability of the nVNS device
- Patient and parent perceptions of the device

Results

Patients (Table 1)

- Eight patients with migraine without aura were enrolled and collectively had 44 attacks that were treated during the 1-month assessment period

Pain Intensity (Figures 2 and 3)

- Of all treated migraine attacks, 47.7% (21/44) were pain free or mild in intensity at 1 hour after nVNS as rated on the VAS and did not require rescue medication (Figure 2)
  - 38.6% (17/44) of the attacks were pain free
  - An additional 9.1% (4/44) were rated as only mild in intensity
- Mean VAS score reductions appeared to be most pronounced when treatment was initiated during milder levels of pain (Figure 3)
- Only 1 attack recurrence within 24 hours was reported by 1 patient who required rescue medication

Safety and Tolerability

- Patients did not report any device-related adverse events
- There were no safety concerns or discontinuations

Device Perceptions

- All patients and/or their parents indicated that the nVNS device was safe and easy to use
- Treatment with nVNS was perceived as useful for 50% of the patients

Table 1. Demographics and Baseline Characteristics

Characteristic	All Patients (N=8)
Female, No. (%)	6 (75)
Age (y), mean ± SD	16.1 ± 1.8
Age at migraine onset (y), mean ± SD	10.5 ± 2.2
Migraine frequency (d/mo), mean ± SD	5.4 ± 1.3[a]
Acute medication use (times/mo)	
NSAIDs, mean ± SD	5.4 ± 1.6[a]
Triptans, mean ± SD	0.1 ± 0.4[a]

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation.
[a] As recorded in patient headache diaries that were completed retrospectively at the start of the assessment period.

Figure 2. Percentages of All Attacks (N=44) That Were Successfully Treated

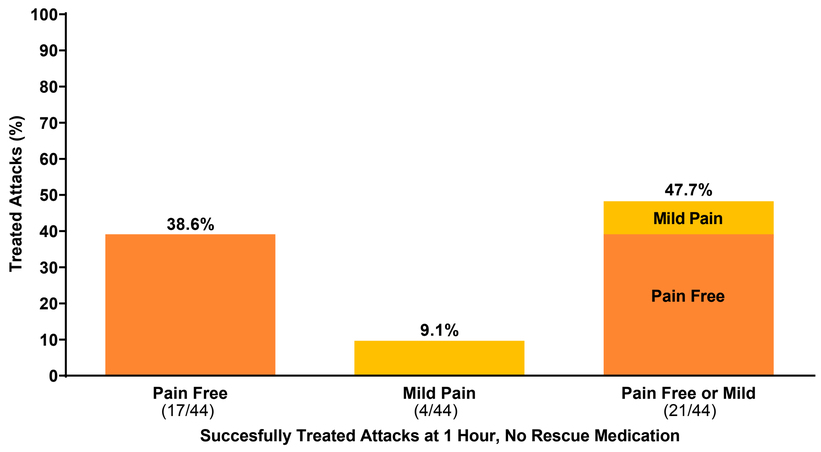
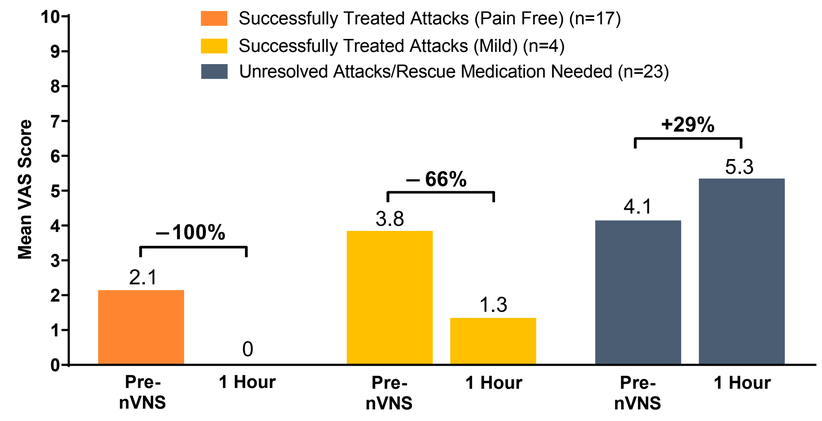


Figure 3. Changes in Mean Pain Intensity at 1 Hour



Abbreviation: VAS, visual analogue scale.

Conclusions

- Use of nVNS in 8 adolescents was safe, well tolerated, and practical for the treatment of migraine without aura
- Acute nVNS treatment was particularly effective and useful for half of the patients, none of whom required rescue medication
- Initiation of nVNS treatment when pain was milder in intensity was more likely to result in a pain-free outcome at 1 hour
  - This finding is consistent with results of previous migraine studies and is particularly relevant given the rapid onset and short duration of attacks that occur in adolescents[14,15]
- Results of this pilot trial are promising, are comparable to open-label data from other sensitive patient populations,[11] and provide a rationale for larger studies of nVNS as a potential acute treatment option for adolescents with migraine

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