Non-invasive Vagus Nerve Stimulation (nVNS) for Treatment of Cluster Headache: Early UK Clinical Experience

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Introduction

- Cluster headache (CH) is a primary headache disorder that is characterised by recurrent attacks of severe pain, is associated with substantial social and economic burdens, and has limited treatment options[1-4]
- A non-invasive vagus nerve stimulation (nVNS) device (gammaCore®) has demonstrated safety and efficacy for prevention and acute treatment of CH attacks[5-7]
  - The device is CE marked and is indicated for acute and/or prophylactic therapy in CH and for treatment of migraine, hemicrania continua, and medication overuse headache in adults
- The National Institute for Health and Care Excellence (NICE) recently published interventional procedure guidance (IPG) for the use of nVNS in CH and migraine[8]
  - Although funding for nVNS is currently not broadly available from the National Health Service (NHS), individual funding requests are considered
- To further explore the UK clinical experience with nVNS, we conducted this audit of data from patients with refractory CH who had successful treatment outcomes during an nVNS evaluation period and for whom NHS funding requests were being compiled

Methods

- Before funding for nVNS was requested, all patients underwent an evaluation period for adjunctive nVNS as prophylactic therapy, acute therapy, or both
  - The following data were collected from patient interviews, treatment diaries, and physician notes
    - Demographics and patient characteristics
    - CH attack frequency, duration, and severity before and after the initiation of nVNS therapy
      - Patients rated attack severity on a scale of 0 to 10, with higher scores indicating greater severity
    - Frequency (i.e. the number and timing of stimulations administered) and duration of nVNS therapy
      - A single stimulation lasted 120 seconds
      - Physicians determined the appropriate nVNS dosing paradigms for their patients
    - Use of preventive and abortive treatments before and after the initiation of nVNS therapy
    - Other effects of nVNS noted by patients and/or physicians in patient interviews, treatment diaries, and physician notes
    - Adverse events (AEs)
- Quantitative information regarding CH duration and severity was unavailable for some patients; such cases were included only in *qualitative* analyses
- Data were summarised with descriptive statistics, and paired *t* tests were used to quantitatively assess within-patient changes in CH attack frequency, duration, and severity before and after adjunctive nVNS therapy
  - Patients who had no attacks during the nVNS evaluation period were excluded from analyses of attack duration and severity as these analyses were contingent on the occurrence of CH attacks while receiving nVNS therapy

Results

- 30 patients from 10 clinical centres throughout England (Table 1)

nVNS Use

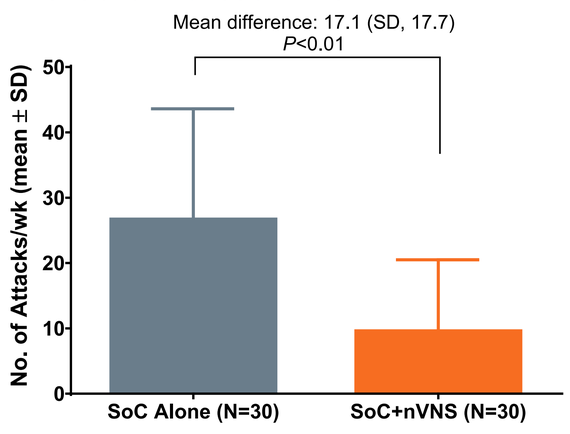
- nVNS evaluation period lasted a mean of 7.6 mo (range, 0.9-27.5 mo)
- 29 patients (97%) used nVNS as prophylaxis
  - Of these, 16 patients (55%) used nVNS as prophylaxis *only*
  - Mean prophylactic stimulation frequency was 5.6 stimulations/d (range, 2.0-9.0 stimulations/d)
  - Most commonly used nVNS prophylactic regimens were
    - 2 consecutive stimulations administered 3 times/d (13 patients)
    - 3 consecutive stimulations administered 2 times/d (8 patients)
- 14 patients (47%) used nVNS for acute treatment
  - All but 1 used nVNS as acute treatment *in addition* to using it as prophylaxis; the remaining patient, who had episodic CH, used nVNS as acute treatment *only*
  - Mean acute stimulation frequency was 4.3 stimulations/d (range, 0.4-18.0 stimulations/d)
  - Most commonly used acute dosing regimen was 3 consecutive stimulations at the onset of each CH attack (10 patients)

Table 1. Demographics and Baseline Characteristics

	nVNS+SoC (N=30)
Age,[a] mean (range), y	47.9 (16.0-72.0)
Female sex, No. (%)	19 (63)
Diagnosis, No. (%)	
Chronic CH	29 (97)
Episodic CH	1 (3)
Time since CH diagnosis,[a,b] mean (range), y	7.2 (0-22)
Failed preventive treatments,[c] mean (range), No.	8.9 (1-16)
Failed acute treatments,[c] mean (range), No.	1.3 (0-4)
Active preventive treatments,[a] mean (range), No.	0.8 (0-2)
Active acute treatments,[a] mean (range), No.	1.8 (1-4)

[a] At the time nVNS therapy was begun. [b] Calculated using the year nVNS was begun minus the year CH was diagnosed.
[c] Refers to treatments used and stopped before nNVS therapy was begun.

Figure 1. CH Attack Frequency With SoC Alone and With SoC+nVNS

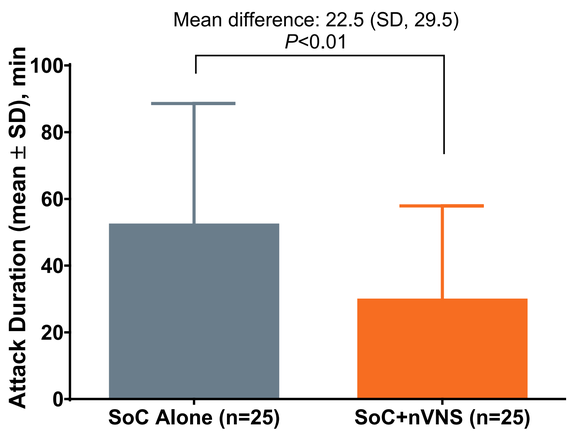


P value is from paired *t* test.

Attack Frequency (Figure 1/Table 2)

- When patients' usual standard of care (SoC) alone was used, the mean CH attack frequency (as reported before the initiation of nVNS therapy) was 26.6 attacks/wk (range, 3.8-77.0 attacks/wk; Figure 1)
  - This decreased significantly ($P<0.01$) to a mean of 9.5 attacks/wk (range, 0-38.5 attacks per week) during the nVNS evaluation period
- 25 of 30 patients (83%) had a decrease in the number of attacks/wk, including the 1 patient who used nVNS as acute treatment only and 3 patients (all with chronic CH) who had no attacks with nVNS therapy (Table 2)
  - 5 patients (17%) reported no change in attack frequency

Figure 2. CH Attack Duration With SoC Alone and With SoC+nVNS



P value is from paired *t* test. Patients who had 0 attacks while using nVNS therapy were excluded.

Attack Duration (Figure 2)

- Of the 26 patients with available qualitative information, 17 (65%) indicated that the duration of their attacks decreased after addition of nVNS; 7 patients (27%) indicated no change, and 2 patients (8%) noted an increase
- Among the 25 patients with available quantitative data, the mean attack duration on SoC alone was 51.9 min (range, 5.0-140.0 min; Figure 2)
  - This decreased significantly ($P<0.01$) to a mean of 29.4 min (range, 2.5-152.5 min) during the nVNS evaluation period

Attack Severity (Figure 3)

- Of the 23 patients with available qualitative data, 17 (74%) indicated that the severity of their attacks decreased after initiation of nVNS; 5 patients (22%) indicated no change, and 1 patient (4%) noted an increase
- Among the 18 patients with available quantitative data, the mean attack severity rating on SoC alone was 7.8 (range, 3.0-10.0; Figure 3)
  - This decreased significantly ($P<0.01$) to a mean of 6.0 during the nVNS evaluation period

Table 2. Summary: Patients Who Were Free of CH Attacks on nVNS Therapy

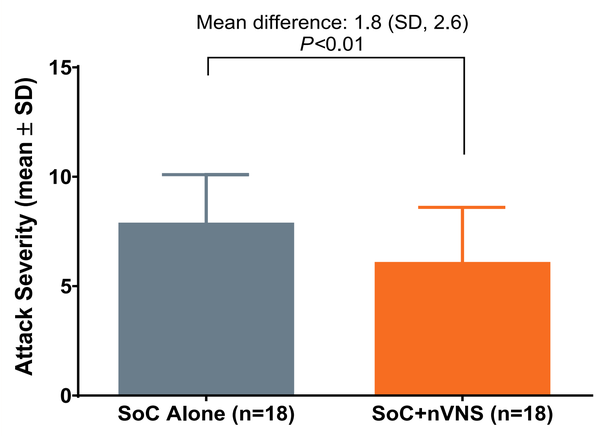
Patient	Year of CH Diagnosis	Initiation of nVNS Therapy	Average No. of Attacks per Week Before Initiation of nVNS Therapy	Duration of nVNS Evaluation Period, mo[a]
A	2009	December 2013	42	13.2
B	2010	September 2015	42	1.7
C	1996	July 2015	63[b]	8.4

[a] Months were classified as 30-day periods; [b] On average, the patient had 63 attacks per week while receiving SoC and 49 attacks per week without treatment.

Use of Concomitant Treatments

- Mean overall number of preventive treatments used was 0.8 (range, 0-2) before initiation of nVNS and 0.7 (range, 0-2) afterward
- Mean number of acute treatments used overall was 1.8 (range, 1-4) before initiation of nVNS and 1.1 (range, 0-2) afterward
- 22 patients (73%) used triptan injection or nasal spray as acute treatment before initiation of nVNS
  - Of these patients, 9 (41%) stopped and 12 (55%) reduced their triptan use after beginning nVNS; triptan use was unchanged in the remaining patient
  - No patients initiated or increased the use of triptan injection or nasal spray while on nVNS
- 27 of 29 patients (93%) used high-flow oxygen acutely before they began nVNS (data unavailable for 1 patient)
  - Among these patients, 9 (33%) stopped high-flow oxygen use and 17 (63%) reduced its use during nVNS therapy; use of this treatment was unchanged in the remaining patient
  - No patients initiated or increased the use of high-flow oxygen while on nVNS

Figure 3. CH Attack Severity With SoC Alone and With SoC+nVNS



Attack severity was rated on a 0 to 10 scale, with higher scores indicating greater severity.
P value is from paired *t* test. Patients with 0 attacks during nVNS therapy were excluded.

Additional Effects of nVNS

- No serious device-related AEs were reported during nVNS therapy
- Considering the outcomes of CH attack *frequency*, *duration*, and *severity*
  - For 28 patients (93%), the number of outcomes that improved with nVNS exceeded the number that worsened
  - One patient had no change in attack frequency, duration, or severity but reported greatly improved quality of life owing to the elimination of interictal pain and increased independence
  - For 1 patient, attack frequency decreased but attack duration and severity increased; however, the patient noted improved quality of life owing to the resolution of AEs associated with SoC
- In addition to improvements in CH attack frequency, duration, and severity, patient-reported benefits associated with nVNS therapy included the following
  - Decreased interictal headache pain (n=6)
  - No longer housebound (n=6)
  - Ability to return to work or school (n=4)
  - Improved sleep (n=4)
  - Increased independence/confidence (n=4)
  - Reduced absenteeism from work (distinct from *ability to return to work or school*; n=4)
  - Need for surgery averted (n=3)

Discussion

- For these 30 patients with treatment-refractory CH, headache burden decreased after the initiation of nVNS therapy (as evidenced by improvements on 1 or more outcomes or additional benefits that reduced the overall need for patient care/support), which led their physicians to request NHS funding for nVNS on their behalf
  - Because of this study's inherent selection bias (i.e. only patients who demonstrated a clinically meaningful response to nVNS therapy were included), responses in these patients are unlikely to represent those of the CH population as a whole
- 3 patients (10%), all with chronic CH, reported being free from CH attacks after beginning nVNS therapy; these cases constitute periods of remission according to *International Classification of Headache Disorders* (3rd edition) criteria,[2] a finding consistent with previous research on neuromodulatory therapy for CH[9]
  - Further research is needed on the effects of continued nVNS therapy during remission periods
- Mounting evidence supports the clinical efficacy and practicality of nVNS for CH and migraine[6,7,10] (also see abstracts by Gaul et al, Grazzi et al, and Nonis et al here at EHMTIC 2016)
  - Although long-term studies of nVNS in CH are limited, some findings suggest that patients who initially respond have a maintained or improved response with longer-term (1-year) therapy[11]
- nVNS also appears to have economic benefits commensurate with its clinical effects
  - Results from a recent pharmacoeconomic modelling analysis of prophylaxis in patients with chronic CH suggest that adjunctive nVNS is more effective and cost saving than SoC alone[12]; reduced use of acute treatments in the current study further support the potential cost-effectiveness of nVNS
- All patients in this study had refractory CH, most having failed multiple preventive and/or acute treatments; however, nVNS therapy could also confer benefit to patients with less refractory or de novo CH who express interest in non-invasive, non-pharmacologic interventions associated with minimal AEs
- The recently published NICE IPG for use of nVNS in CH and migraine suggests no major safety concerns but notes limited evidence of efficacy[8]
  - Because the NHS is not legally obligated to fund treatments recognised by NICE IPG, patients may experience difficulties in accessing potentially beneficial novel technologies
  - Guaranteed NHS funding would require NICE technology appraisal guidance (TAG) based on a review of clinical and economic evidence supporting nVNS use[13]
- As the body of data demonstrating the efficacy and safety of nVNS in CH continues to grow, broader guidance and support (e.g. NICE TAG) for this technology are warranted

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