

## Non-invasive vagus nerve stimulation is beneficial in chronic paroxysmal hemicrania

### INTRODUCTION

Paroxysmal hemicrania (PH) is a rare primary headache disorder characterised by recurrent attacks of severe, strictly unilateral pain, focused around the orbital, supraorbital and temporal regions and associated with autonomic features. Attacks usually occur more than five times a day and last 2–30 min.<sup>1</sup> The disorder has an absolute response to indomethacin such that patients are rendered pain-free by therapeutic doses. Between 65% and 88% of patients suffer

from the chronic form of PH where the attacks occur for more than 1 year without remission or with remission periods lasting less than 3 months.<sup>2</sup> Over 30% of patients report dose-limiting side-effects with indomethacin and approximately 20% discontinue the drug due to tolerability problems.<sup>3</sup> Although several other drugs have been reported to have efficacy in PH, none offer the same magnitude of response.

Evidence to support the role of the vagus nerve in trigeminal pain have been identified in prior studies. Inhibition of nociceptive activation of the trigeminocervical neurons have been shown in preclinical animal models, with a dose-dependent effect.<sup>4</sup> Non-invasive vagus nerve stimulation (nVNS), using the gammaCore device, has been reported to be beneficial in trigeminal autonomic cephalalgias (TACs). A recent audit looking at 15 patients with indomethacin-responsive headaches, six of whom had PH, concluded that nVNS may be an important adjunct or alternative in those patients with TACs.<sup>5</sup>

### METHOD

Given these results, we tried nVNS in eight chronic paroxysmal hemicrania (CPH) patients who were intolerant of indomethacin. Patients were diagnosed as CPH based on ICHD-3 beta criteria.<sup>1</sup> At initial presentation, some patients reported attacks lasting more than 30 min though most of the attacks lasted less than 30 min; occasional prolonged attacks are a common feature in PH.<sup>2</sup> Prior to use, all patients had complete suppression of headaches with indomethacin but experienced significant side effects. One patient was on a stable dose of pregabalin prior to starting nVNS, the remainder were not on concomitant medication use. Treatment with nVNS was offered as a 'humanitarian intervention' and ethics board approval for the collection and publication of data was granted by Northwick Park Hospital Research Ethics Committee, Hampstead, London, UK (REC Number. 11/LO/1709).

Patients administered two consecutive doses three times a day ipsilateral to the pain. The stimulator has a predetermined duration of 2 min and patients can change the stimulation intensity. The patients in this group were asked to increase the stimulation until the point of 'lip pull' to ensure optimal stimulation. They were trained on how to use the device and their technique was checked 4 weeks

**Table 1** Non-invasive vagal nerve stimulation in chronic paroxysmal hemicrania

Patient number	1	2	3	4	5	6	7	8
Age	52	52	28	20	43	44	81	63
Sex	Male	Male	Male	Female	Female	Male	Male	Female
Duration of CPH (years)	3	11	3	6	22	11	8	5
Headache characteristics at diagnosis								
Frequency	8–12/day	6–8/day	5–9/day	4–13/day	10–20/day	5–20/day	4–12/day	5–12/day
Severity (VRS)	10	5–10	7–10	8–10	6–10	4–8	10	8–10
Duration (min)	15–30	15–45	15–60	15–120	5–90	5–120	5–20	5–45
Median duration (min)	20	20	25	20	10	30	15	15
Indometacin dose	225 mg	100 mg	225 mg	75 mg	225 mg	225 mg	100 mg	225 mg
Side effects from indometacin	Severe lethargy	colitis	Severe gastrointestinal upset	Severe gastrointestinal upset	Swollen ankles and marked lethargy	Severe gastrointestinal upset	Duodenal ulcer	Severe gastrointestinal upset
Preventive treatments failed	3	4	3	3	4	5	3	1
Duration of use of VNS (months)	19	10	6	6	7	5	7	3
Baseline headaches (1 month pre-VNS)								
Frequency	5–10/day	2–3/day	5/day	1–2/day	5/day	2/day	4–5/day	2–5/day
Severity (VRS)	10	2–6	7–8	8–10	4–8	5–9	10	9–10
Duration (min)	20–30	30–90	45–60	15–120	5–80	60–120	15–20	30–45
Follow-up at 3 months								
Frequency	2–3 week	1/day	2/week	5/month	1/day	1–2/day	0	2–5/day
Severity (VRS)	5–6	2–3	4–5	5–9	1–2	1–2	0	9–10
Duration (min)	15–20	30–60	20–30	5–20	5–30	30–60	0	30–45
Follow-up at 6 months								
Frequency	1/week	1/day	2/week	5/month	0	N/A	0	N/A
Severity (VRS)	6–7	2–4	4–5	5–9	0	N/A	0	N/A
Duration (min)	15–20	30–60	20–30	5–20	0	N/A	0	N/A
Last follow-up								
Frequency	1/week	1/day	2/week	5/month	0	1–2/day	0	2–5/day
Severity (VRS)	6–7	2–4	4–5	5–9	0	1–2	0	9–10
Duration (min)	20	30–60	20–30	5–20	0	30–60	0	30–45
HIT-6								
Baseline	70	59	69	74	50	48	40	74
3 months	60	55	59	31	46	48	36	76
6 months	65	54	59	30	36	N/A	36	N/A
Last follow-up	66	54	59	30	36	48	36	N/A
MIDAS								
Baseline	21	5	190	71	81	0	0	105
3 months	4	5	167	68	0	0	0	120
6 months	18	5	78	67	0	N/A	0	N/A
Last follow-up	14	5	78	67	0	0	0	N/A
HADS-A								
Baseline	2	9	12	17	20	2	1	18
3 months	6	6	4	18	19	0	0	17
6 months	5	6	0	19	19	N/A	0	N/A
Last follow-up	3	6	0	19	19	0	0	N/A
HADS-D								
Baseline	3	6	14	14	16	2	1	15
3 months	1	5	7	14	9	0	0	16
6 months	3	5	0	15	9	N/A	0	N/A
Last follow-up	6	5	15	15	9	0	0	N/A
Patients estimate of improvement	70%	70%	90%	80%	100%	65%	100%	0%

CPH, chronic paroxysmal hemicrania; HADS-A/D, Hospital Anxiety and Depression Scale—Anxiety/Depression; HIT-6, Headache Impact Test-6; MIDAS, Migraine Disability Assessment; N/A, no data available; VNS, vagus nerve stimulation; VRS, verbal rating scale (0–10; 0 pain free, 10 very severe pain).

later to ensure it was optimal. Prospective headache diaries were kept at baseline and throughout follow-up. Patients were followed up every 3–6 months when data were collected on headache disability scores (Migraine Disability Assessment Score (MIDAS) and Headache Impact Test (HIT-6) and affective measures (Hospital Anxiety and Depression Scale (HADS)).

ElectroCore supplied the devices through a cost sharing programme; the device was supplied free of charge for 3 months and thereafter the device was paid for either by the patient or the healthcare provider.

## RESULTS

The results of this case series are shown in table 1. The group consisted of eight patients (five males) with a mean age of 48 years (range: 20–81 years) and median duration of CPH of 8 years (range 3–22 years). Patients had failed to respond to an average of three preventive medications (range: 1–5) and all had dose limiting side effects to indomethacin. Median follow-up of the cohort was 7 months (3–19 months). At 3 months, the mean monthly headache frequency fell by 68.01% ( $p=0.012$ ) but further dropped to 75% ( $p=0.003$ ) at the final follow-up. A favourable response, defined as a more than 50% reduction in monthly headache frequency, was observed in 75% of patients at final follow-up. The median time to reach a 50% improvement was 3 months (range: 3–6 months). There was a reduction in median severity of attacks from verbal rating score (VRS) 8/10 to 6/10 ( $p=0.050$ ) at 3 months follow-up. At final follow-up, the median severity of attacks dropped from VRS 8/10 to 4/10 ( $p=0.011$ ). Similarly, there was a reduction in the median duration of attacks from 47.5 min to 21.25 min at 3 months follow-up ( $p=0.007$ ) and at final follow-up to 23.1 min ( $p=0.007$ ). Significant reductions were reported in HIT-6 and MIDAS scores. Seven patients showed a reduction in the Hospital Anxiety (HAD-A) scores, while four patients showed a reduction in the Hospital Depression (HAD-D) scores.

The average estimated global improvement was 64.37% and 71.88% at 3 months and final follow-up, respectively. No adverse events were reported by any patients.

## DISCUSSION

Our experience suggests that nVNS has potential use as a preventative therapy for PH in patients unable to tolerate indomethacin. As detailed above, six of the eight patients had more than 50% reduction in frequency in their monthly headaches with significant improvements in their disability scores. We identified a 75% favourable response with two patients becoming attack-free.

There are limitations to these data, including those inherent to any unblinded series, though despite this our results are encouraging. The strength of the current series includes the use of prospective data. Further research into the use and safety of nVNS in PH is required. However, given the rarity of PH, it is unlikely that an adequately powered, randomised controlled trial will occur in the near future. Our results nonetheless highlight the potential importance of nVNS in this patient group and also the need to ensure patients adhere to treatment for at least 3 months given the latency to median treatment efficacy.

## CLASSIFICATION OF EVIDENCE

Class IV.

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## REFERENCES

- 1 Headache Classification Subcommittee of The International Headache Society. *The international classification of headache disorders*. 3rd edn, 2013: 629–808.
- 2 Cittadini E, Matharu MS, Goadsby PJ. Paroxysmal hemiparesis: a prospective clinical study of 31 cases. *Brain* 2008;131:1142–55.
- 3 Dodick DW. Indomethacin-responsive headache syndromes. *Curr Pain Headache Rep* 2004;8:19–26.
- 4 Akerman S, Simon B, Romero-Reyes M. Vagus nerve stimulation suppresses acute noxious activation of trigemino-cervical neurons in animal models of primary headache. *Neurobiol Dis* 2017;102:96–104.
- 5 Tso AR, Marin J, Goadsby PJ. Noninvasive vagus nerve stimulation for treatment of indomethacin-sensitive headaches. *JAMA Neurol* 2017;74:1266–7.