Safety and efficacy of sphenopalatine ganglion stimulation for chronic cluster headache: a double-blind, randomised controlled trial

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Summary

Background Chronic cluster headache is the most disabling form of cluster headache. The mainstay of treatment is attack prevention, but the available management options have little efficacy and are associated with substantial side-effects. In this study, we aimed to assess the safety and efficacy of sphenopalatine ganglion stimulation for treatment of chronic cluster headache.

Methods We did a randomised, sham-controlled, parallel group, double-blind, safety and efficacy study at 21 headache centres in the USA. We recruited patients aged 22 years or older with chronic cluster headache, who reported a minimum of four cluster headache attacks per week that were unsuccessfully controlled by preventive treatments. Participants were randomly assigned (1:1) via an online adaptive randomisation procedure to either stimulation of the sphenopalatine ganglion or a sham control that delivered a cutaneous electrical stimulation. Patients and the clinical evaluator and surgeon were masked to group assignment. The primary efficacy endpoint, which was analysed with weighted generalised estimated equation logistic regression models, was the difference between groups in the proportion of stimulation-treated ipsilateral cluster attacks for which relief from pain was achieved 15 min after the start of stimulation without the use of acute drugs before that timepoint. Efficacy analyses were done in all patients who were implanted with a device and provided data for at least one treated attack during the 4-week experimental phase. Safety was assessed in all patients undergoing an implantation procedure up to the end of the open-label phase of the study, which followed the experimental phase. This trial is registered with ClinicalTrials.gov, number NCT02168764.

Findings Between July 9, 2014, and Feb 14, 2017, 93 patients were enrolled and randomly assigned, 45 to the sphenopalatine ganglion stimulation group and 48 to the control group. 36 patients in the sphenopalatine ganglion stimulation group and 40 in the control group had at least one attack during the experimental phase and were included in efficacy analyses. The proportion of attacks for which pain relief was experienced at 15 min was 62·46% (95% CI 49·15–74·12) in the sphenopalatine ganglion stimulation group versus 38·87% (28·60–50·25) in the control group (odds ratio 2·62 [95% CI 1·28–5·34]; p=0·008). Nine serious adverse events were reported by the end of the open-label phase. Three of these serious adverse events were related to the implantation procedure (aspiration during intubation, nausea and vomiting, and venous injury or compromise). A fourth serious adverse event was an infection that was attributed to both the stimulation device and the implantation procedure. The other five serious adverse events were unrelated. There were no unanticipated serious adverse events.

Interpretation Sphenopalatine ganglion stimulation seems efficacious and is well tolerated, and potentially offers an alternative approach to the treatment of chronic cluster headache. Further research is need to clarify its place in clinical practice.

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Introduction

Cluster headache is a trigeminal autonomic cephalalgia.[1] It has an episodic subtype, in which patients go at least 3 months attack free and without treatment during any 12-month period, and a chronic subtype, in which patients have no such break from treatment. Acute attacks of cluster headache can typically occur from every second day to eight times a day, in association with cranial autonomic features ipsilateral to the pain.[2] Roughly 20% of all patients with cluster headache have the chronic subtype.[3] The 1-year combined population prevalence of episodic and chronic cluster headache is estimated to be 0·1%.[4] Acute attacks can occur with clockwork-like regularity, including attacks that frequently awaken patients from sleep.[5] Remarkably, acute cluster headache attacks are considered to be the worst pain that human beings experience.[6]

Patients with chronic cluster headache need both preventive and acute treatment options. Options for acute

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Research in context

Evidence before this study

We searched Embase and MEDLINE with the terms "cluster headache" and "trigeminal autonomic cephalalgias" for articles published in English up to Jan 31, 2019. We also hand searched abstracts from meetings of the International Headache Society, American Headache Society, Migraine Trust, and European Headache Federation from the past 10 years. Chronic cluster headache is a highly disabling primary headache disorder that is often refractory to treatment. We identified one previous small blinded phase 2 study of sphenopalatine ganglion stimulation (CH-1), in which the therapy was efficacious compared with an inactive sham. This finding raised the question of whether efficacy would be maintained in a trial with adequate blinding. A limitation of our search strategy is that unreported negative trial results might not have been identified.

Added value of this study

This well blinded study provides further evidence that stimulation of the sphenopalatine ganglion in patients with chronic cluster headache can both control acute cluster headache attacks and diminish the frequency of attacks over time.

Implications of all the available evidence

The evidence from this trial, together with long-term safety data from the CH-1 study, suggests that sphenopalatine ganglion stimulation could be a promising option for management of chronic cluster headache.

attacks include triptans, serotonin 5-HT_{1B} and 5-HT_{1D} receptor agonists[3], and inhaled oxygen.[7] Triptans have cardiovascular contraindications[8] that are important in cluster headache, which affects three times as many men as women and is common in people older than 50 years with a history of cigarette smoking.[4] The mainstay of preventive treatment in chronic cluster headache is high-dose verapamil (up to 960 mg daily), which has well recognised side-effects, including cardiac arrthymias.[9] Non-invasive neuromodulation approaches to treatment of acute cluster headache have been developed in the form of non-invasive vagal nerve stimulation, but this treatment did not work in patients with chronic cluster headache in two separate studies.[10,11] Invasive neuromodulation approaches, such as occipital-nerve stimulation,[12,13] have been used with some efficacy, but no controlled trial data are available. Deep-brain stimulation[14] has also been used in chronic cluster headache, with patients accepting the associated risk of death[15] to avoid further attacks.

An important component of the pathophysiology of acute cluster headache attacks is activation of the trigeminal–autonomic reflex,[16] which accounts for the cranial autonomic features, such as lacrimation, conjunctival injection, nasal congestion, aural fullness, and periorbital oedema. The outflow pathway for these symptoms traverses the facial nerve (ie, the seventh cranial nerve) and synapses in the sphenopalatine ganglion,[17] which is located in the pterygopalatine fossa.[18] On the basis of this anatomy and clinical experience, the sphenopalatine ganglion was postulated to be a therapeutic target,[19–21] and a sphenopalatine ganglion stimulator was subsequently developed and studied. In the first phase 2 trial,[22] which included 32 patients with chronic cluster headache, the sphenopalatine ganglion stimulator was compared with a sham with no stimulation and a subperception stimulus in a randomised crossover design. In the sphenopalatine ganglion stimulator group, pain relief at 15 min was experienced in 67% of attacks, compared with 7% of attacks in both the sham and subperception treatment groups. 36% of participants in the sphenopalatine ganglion stimulator group also reported a 50% or greater reduction in attack frequency.[22] However, this study was limited by its small size and the use of a no-perception sham.

Building on this previous study, we sought to establish the safety and efficacy of sphenopalatine ganglion neurostimulation for the acute treatment of attacks in patients with chronic cluster headache in a trial with better blinding.

Methods

Study design and participants

We did a randomised, sham-controlled, parallel group, double-blind, safety and efficacy study at 21 headache centres in the USA. Eligible participants were aged 22 years or older and had chronic cluster headaches[2] (at least four attacks per week, on the side of their dominant headache laterality) that were judged by investigators and participants to be either previously or currently inadequately controlled with available therapies (in terms of both prevention and treatment of acute attacks). Exclusion criteria included change in type, dose, or dose frequency of preventive headache drugs within the month before enrolment, or a previous diagnosis of trigeminal neuralgia or other trigeminal autonomic cephalalgias (eg, paroxysmal hemicrania, short-lasting unilateral neuralgiform headache with conjunctival injection and tearing). A full list of inclusion and exclusion criteria is provided in the appendix (pp 1–3).

See Online for appendix

Investigators identified potential participants and passed screening data to PJG and DWD, who reviewed the data and decided whether the person should be included in the study (both reviewers needed to agree on inclusion). The study was done in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The trial protocol received approval from the institutional review board at each participating centre. Patients provided

written, informed consent before being screened for eligibility.

Randomisation and masking

Eligible participants were randomly assigned (1:1) to receive either sphenopalatine ganglion stimulation or sham stimulation (ie, the control group). Patients were randomly assigned automatically, one by one, by an unblinded study coordinator at each participating site, who used the Bracket Global software system. An adaptive randomisation procedure was used to allocate patients to result in the least possible imbalance between groups in terms of the covariates investigational site (surgical site), sex, and overall (ie, ipsilateral and contralateral) weekly attack frequency (≤56 *vs* >56), in that order of priority. The Bracket Global software system took into account the final allocation of the previous randomly assigned participant to adaptively assign each subsequent patient. In this implementation of the adaptive randomisation method, imbalance was calculated for each covariate and each potential therapy allocation with the χ^2 method.

Participants were masked to group allocation, with cutaneous surface stimulation used to optimise the blinding.[23] They were also actively asked not to discuss their allocation or progress on social media to facilitate maintenance of the blinding.[24] At least one person at each study site was blinded to patients' allocation to enable administration of blinded patient interviews, quality-of-life questionnaires, and other patient assessments. The study statistician and the core laboratory responsible for assessing neurostimulator lead position were also blinded to group assignments. The randomisation list was not unblinded until during final analyses. Blinding was assessed with the James' Blinding Index, on which scores range from 0 (total absence of blinding) to 1 (complete blinding); scores of 0·5 or higher have been used as support for adequate blinding.[25] The blinding index value was 0·63 in our study.

Procedures

The study consisted of five phases after enrolment: the baseline phase (at least 4 weeks), during which diary information was recorded to confirm patients' eligibility; the stabilisation phase (12 weeks), which was after randomisation and implantation of study or sham devices but before activation, to allow for healing; the parameter adjustment phase (12 weeks), when stimulation parameters were adjusted (with sham adjustment in the control group); the experimental phase (4 weeks), when attacks could be treated with the device; and the open-label phase, during which all patients were treated with sphenopalatine ganglion stimulation, and in which collection of stimulation and diary data continued for 1 year after implantation, followed by an optional long-term follow-up period (appendix p 10).

After eligibility was confirmed, patients were implanted with either the Autonomic Technologies Sphenopalatine Ganglion Neurostimulation System (Mountain View, CA, USA) or a corresponding sham treatment by 13 implanting surgeons. The implantation procedure has been described previously.[26] The ATI Sphenopalatine Ganglion Neurostimulation System consists of the stimulator, a miniaturised implant with an integral lead with six stimulating electrodes (figure 1A); a handheld remote controller (figure 1B), which activates and controls the stimulator, and acts as a diary to record symptoms and treatment given; surgical tools and an introducer and lead blank, which are used during the implantation; and software to test and program the stimulator and set the power level in the remote controller. Power is supplied to the lead by the remote controller so there is no implanted battery. Figure 2 shows the relevant anatomy.

During the parameter adjustment and experimental phases, participants were asked to treat acute cluster headache attacks of at least moderate severity for 15 min with their implanted device before using any other acute treatments, such as triptans or inhaled oxygen. If pain relief was not adequate at 15 min, they were permitted to use their usual acute treatment. After completion of the assessments for any attack at 1 h, any new qualifying attack with pain of moderate or greater intensity that occurred after the patient had been pain free could be treated with the trial stimulation. The remote controller recorded pain ratings and medications use at 15 min and 1 h after stimulation. Daily diaries were reviewed at all study visits to collate information on headaches and medication use.

Outcomes

In this Article, we report primary and secondary efficacy outcomes for the 4-week experimental phase and safety outcomes to the end of the open-label phase. We grouped efficacy outcomes into two broad categories: attack-level outcomes and patient-level outcomes. The primary efficacy outcome was an attack-level outcome—ie, the proportion

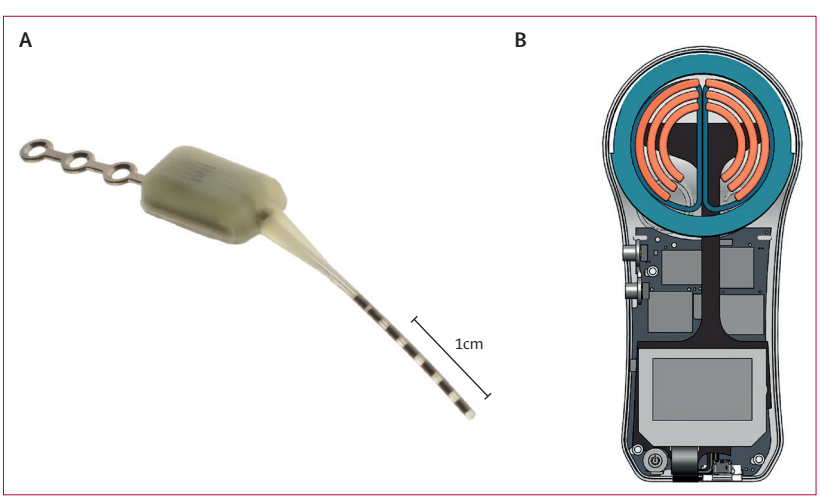

Figure 1: **The sphenopalatine ganglion stimulation system stimulator (A) and remote controller (B)**

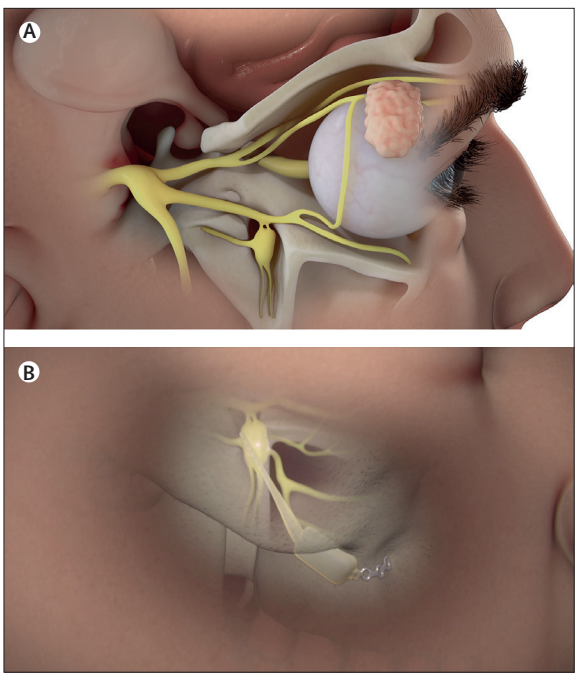

Figure 2: **Anatomy relevant to implantation of the sphenopalatine ganglion stimulation system**

of ipsilateral cluster attacks for which pain relief was achieved 15 mins after starting stimulation. Freedom from pain 15 minutes after starting stimulation was a secondary attack-level efficacy outcome. Both pain relief and freedom from pain were binary outcomes (0 [not achieved] *vs* 1 [achieved]) that were derived from patient reports on a 5-point ordinal pain scale (ranging from 0 [no pain] to 4 [very severe pain]) entered using the remote controller device.[27] Pain relief was defined as a reduction in pain associated with an ipsilateral cluster headache attack from at least moderate severity (ie, pain scores of 2–4) to pain scores of 0 or 1 without the use of acute medications. Freedom from pain was defined as a reduction from pain scores 2–4 to pain score 0 without the use of acute medications. Sustained pain relief (ie relief that was maintained from 15 min to 1 h) was a prespecified ancillary outcome that was also examined for each treated ipsilateral cluster headache attack. Sustained pain relief was a binary outcome for which success was defined as an attack with successful relief of pain at 15 min with lasting pain relief at 1 h.

For patient-level efficacy outcomes, we examined prespecified ancillary outcomes and post-hoc outcomes related to consistency of response in terms of pain relief, freedom from pain, and reduction in the frequency of ipsilateral cluster headache attacks. Acute pain relief and freedom from pain responder status were defined on the basis of the proportion of treated ipsilateral cluster headache attacks for which pain relief or freedom, respectively, were achieved during the experimental phase. Specifically, for patients with at least six treated attacks, those who had pain relief at 15 min after 50% or more attacks were deemed to be responders, whereas those who experienced pain relief for less than 50% of attacks were non-responders. For sustained pain relief, patients who experienced pain relief at both 15 min and 1 h for at least 50% of stimulation-treated attacks during the experimental phase were classified as responders. For attack frequency, patients who had a reduction in their median number of weekly attacks by 50% or more (for the last 4 weeks of the baseline phase compared with the experimental phase, based on daily headache diaries) were classified as responders, whereas those with reductions of less than 50% were non-responders. Although not prespecified, we also examined responders for attack frequency with 75% or 100% reduction thresholds. An additional non-specified outcome was change in median weekly attack frequency. Patients had to have non-missing daily reports for more than half of the eligible within-phase days to compute a weekly median for attack frequency outcomes.

Data for all adverse events were collected. Adverse events that were possibly, probably, or highly probably related to the study device or procedure were classified as related adverse events whereas those that were unlikely to be related or not related to the study device or procedure were classified as unrelated adverse events. A serious adverse event was defined as any adverse event that led to death, serious deterioration in health of the participant (ie, that resulted in a life-threatening illness or injury, permanent impairment of a bodily structure or function, inpatient treatment or prolonged hospitalisation, or medical or surgical intervention to prevent life-threatening illness or injury), or fetal distress, fetal death, or congenital abnormalities or birth defects. All serious adverse events were adjudicated by an independent clinical events committee. A full list of other ancillary endpoints investigated is detailed in the appendix (pp 4–6).

Statistical analysis

The power calculation for this study was based on pain relief at 15 min being experienced for 55% of attacks in patients in the sphenopalatine ganglion stimulation group and 32% of attacks in patients in the control group, and a within-patient correlation of 0·47, with three attacks per patient. Given the nested study design for the experimental phase (ie, multiple attacks reported for each patient), the within-participant correlation represents correlation across attacks within each patient and was assumed to be moderate in magnitude on the basis of our clinical hypothesis. We assumed three attacks per patient, which we conservatively set as a lower estimate of how many attacks patients would report during the experimental period. Power was set to 90%, with a two-sided α of 0·05. Under these assumptions, we estimated that a sample size of 30 patients per group would be required. To account for up to 30% of enrolled patients ultimately not being implanted with the device, and a fall out of approximately 30% after

implantation, a total sample size of 172 patients was recommended.

The study included a prespecified interim assessment of the primary endpoint. A group sequential design following the Pocock Rule was used to establish the stopping boundary at the interim analysis and the final analysis, while maintaining the required overall α of 0·05 for the study. After adjustment for the final analysis, we calculated that an α less that 0·015 was required to meet the primary endpoint. Interim analyses were not done for any other endpoints, and thus these endpoints were tested at a two-sided α of 0·05. We revised our sample size estimation on the basis of the results of the interim analysis, and the number of participants required to meet significance for the primary endpoint were reduced from initial estimates.

Unless otherwise indicated, all analyses were done in the full analysis set, which included all patients who were implanted with a device and provided data for at least one treated attack during the experimental phase. An assessable attack was defined as a cluster headache of at least moderate intensity with a stimulation duration of longer than 3 min and a maximum amplitude of greater than 0 mA.

Treatment differences in attack-level efficacy outcomes were analysed with weighted generalised estimated equation logistic regression models. Briefly, this approach was used to account for nested data structure (ie, multiple attacks per patient) and because the expected number of treated attacks per patient could vary greatly, making the number of attacks potentially informative. The models used a logit link function and binomial response distribution to account for the binary response scales of the outcomes. Generalised estimated equation models were necessary to account for intra-participant association across repeated attacks and to draw appropriate population average inferences. They were also used to generate model-implied predicted values and odds ratios (ORs) that were adjusted for the nested study design. In all models, treatment group was the independent variable and pain relief, freedom from pain, and sustained pain relief were the dependent variables. The weighted generalised estimated equation logistic regression models included all available data for treated attacks from the experimental phase.

For the patient-level efficacy analyses, between-group differences in acute pain relief responders and attack frequency responders were analysed with exact logistic regression models, in which treatment group was the independent variable. Because several of the higher threshold responder definitions (ie, 75% and 100% responders) had small cell sizes, we used exact logistic regression, which is a more robust than standard logistic regression in this setting. The sparseness and reduced sample size (ie, of person-level data compared with attack-level data) led to increased CIs. Group differences for changes in median weekly attack frequency and acute medication use (and acute triptan use specifically) between the baseline phase and the experimental phase were analysed with independent group *t* tests. For robustness, between-group differences in attack frequency were also examined via analysis of covariance (ANCOVA), in which the median weekly attack frequency during the experimental phase was compared. The ANCOVA approach accounts for baseline differences in attack frequency, which can easily be detected in cluster headache and which would potentially complicate the interpretation of change scores. These hypotheses were considered exploratory and were tested at a two-sided α of 0·05.

Safety outcomes were reported descriptively with standard summary statistics. Descriptive statistics and analyses included all available data. All analyses were done in SAS (version 9.4). This trial is registered with ClinicalTrials.gov, number NCT02168764.

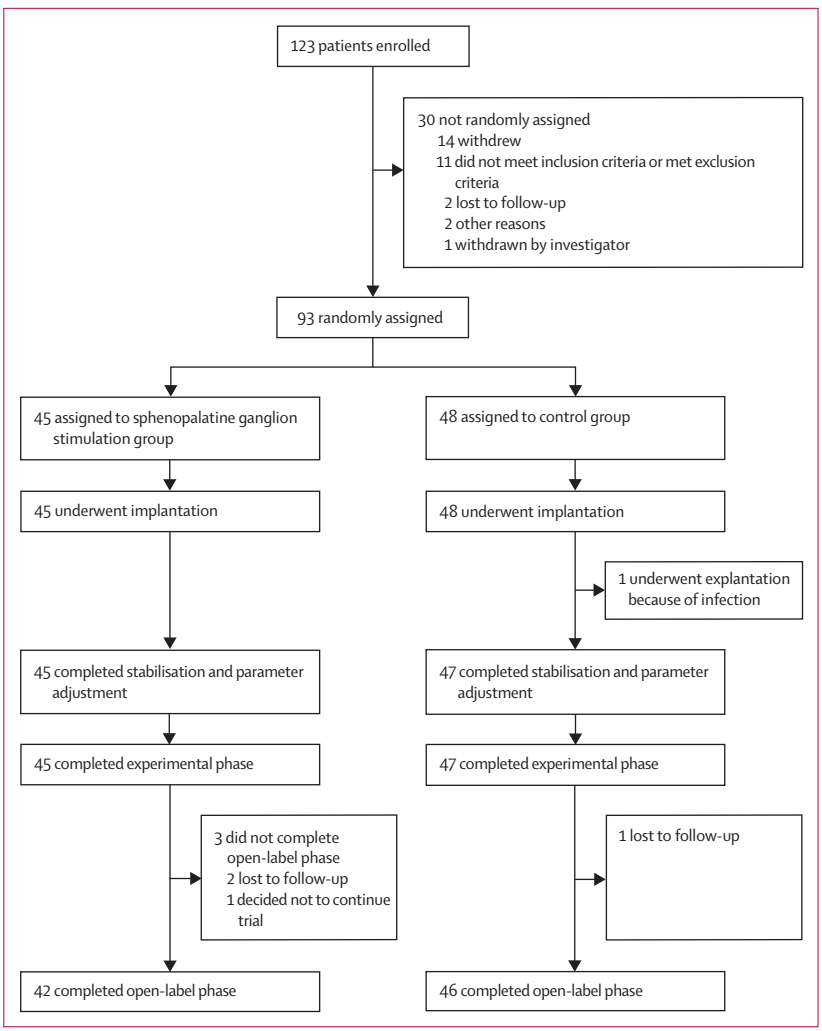

Figure 3: **Trial profile**

Role of the funding source

The funder of the study had roles in study design, data collection, data analysis, data interpretation, and writing

of the report. The corresponding author and DWD had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between July 9, 2014, and Feb 14, 2017, 93 patients were included and randomly assigned, 45 to the sphenopalatine ganglion stimulation group and 48 to the control group (figure 3). Table 1 shows participant demographics. 17 patients, nine in the sphenopalatine ganglion stimulation group and eight in the control group, had no acute attacks during the experimental phase. The remaining 76 participants treated at least one attack during the experimental phase of the trial and used the remote-control device to report pain, and thus were included in the acute pain relief and freedom from pain analyses (ie, the full analysis set).

	Sphenopalatine ganglion stimulation group (n=45)	Control group (n=48)
Age, years	48 (11)	48 (11)
Sex		
Female	12 (27%)	13 (27%)
Male	33 (73%)	35 (73%)
Duration of cluster headache history, years	11 (1–38)	14 (2–44)
No more than 56 cluster headaches per week	45 (100%)	48 (100%)
Cluster attacks per week (during past 4 weeks)	14 (4–50)	14 (2–35)
Peak intensity of cluster attacks during past 4 weeks		
Moderate	12 (27%)	7 (15%)
Severe	22 (49%)	21 (44%)
Very severe	11 (24%)	20 (42%)
Duration of cluster headache attacks during past 4 weeks (despite intervention), mins	45 (10–180)	45 (10–180)
Cranial autonomic symptoms with cluster attacks	45 (100%)	48 (100%)
Previously used at least one preventive medicine unsuccessfully	44 (98%)*	48 (100%)

Data are mean (SD), n (%), or median (range). *Unsuccessful previous use of at least one preventive medicine was an inclusion criterion, but one patient not meeting this criterion was enrolled in error.

Table 1: **Baseline demographics**

Demographic characteristics of the full analysis set (appendix p 6) were similar to those of the full sample. These 76 patients experienced 992 attacks during the experimental phase—a median of ten attacks per patient (IQR 4–19; range 1–64). 91 patients were included in the attack frequency analyses (45 in the sphenopalatine ganglion stimulation group and 46 in the control group). Details of the populations included in the various ancillary and post-hoc analyses are presented in the appendix (p 11).

During the experimental phase, the sphenopalatine ganglion stimulation group were more likely to have pain relief from attacks at 15 min than the control group in weighted generalised estimated equation logistic regression model analyses (OR 2·62 [95% CI 1·28–5·34]; p=0·008; table 2). The model-implied pain relief percentages (ie, the proportions of attacks for which pain relief was experienced at 15 min) were 62·46% (95% CI 49·15–74·12) for the sphenopalatine ganglion stimulation group versus 38·87% (28·60–50·25) for the control group. The sphenopalatine ganglion stimulation group were also more likely to have freedom from pain at 15 min (OR 2·32 [1·06–5·08; p=0·04) and sustained pain relief at 1 h (2·78 [1·37–5·62]; p=0·004) than the control group (table 2).

For the patient-level efficacy outcomes, the sphenopalatine ganglion stimulation group had significantly greater proportions of responders with pain relief at 15 min (OR 4·04 [95% CI 1·13–15·73]; p=0·03), freedom from pain at 15 min (4·84 [1·00–32·20]; p=0·049), and sustained pain relief (10·26 [2·19–68·28]; p=0·001) after 50% or more of attacks than the control group (table 3). Post-hoc analyses provided some evidence showing that the sphenopalatine ganglion stimulation group also had a significantly higher proportion of patients with pain relief at 15 min after at least 75% of attacks (6·72 [1·44–44·50]; p=0·01) and a reduction in the median frequency of attacks by at least 75% (2·92 [1·11–8·07]; p=0·03) compared with the control group (figure 3; appendix p 12).

In a post-hoc analysis of between-group differences in the change between the baseline phase and the experimental phase, sphenopalatine ganglion stimulation seemed to

	Unadjusted analysis		Generalised estimated equation model			
	Sphenopalatine ganglion stimulation group	Control group	Sphenopalatine ganglion stimulation group	Control group	Odds ratio	p value
Pain relief at 15 min	189/410 (46%)	226/582 (39%)	62·46% (49·15–74·12)	38·87% (28·60–50·25)	2·62 (1·28–5·34)	0·008
Freedom from pain at 15 min	123/410 (30%)	125/582 (21%)	40·25% (28·16–53·66)	22·54% (14·14–33·95)	2·32 (1·06–5·08)	0·04
Sustained pain relief at 1 h	165/408 (40%)	175/576 (30%)	56·62% (44·10–68·35)	31·95% (22·28–43·46)	2·78 (1·37–5·62)	0·004

Data are n/N (%), whereby n is the number of attacks with successful outcomes and N is the total number of attacks, or % (95% CI). Data from the generalised estimated equation model take into account the within-person correlation across attacks (ie, nesting of multiple attacks for each patient). The quasi-likelihood under the independence model criterion goodness-of-fit statistics for generalised estimated equation models was 103·46 for pain relief, 93·72 for freedom from pain, and 101·66 for sustained pain relief.

Table 2: **Attack-level efficacy outcomes**

be associated with a reduction in the median weekly frequency of ipsilateral cluster headache attacks compared with sham treatment (mean change –6·84 *vs* –2·60; difference –4·24 [95% CI –7·14 to –1·33]; p=0·005). There was a between-group difference in the frequency of attacks at baseline (mean 13·46 in the sphenopalatine ganglion stimulation group *vs* 9·41 in the control group; between-group difference 4·05 [95% CI 0·29–8·10]; p=0·04). An ANCOVA model, in which these baseline differences were controlled for, showed that sphenopalatine ganglion stimulation treatment seemed to be associated with a lower predicted frequency of attacks than the sham treatment (between-group difference –2·93 [95% CI –5·64 to –0·22]; p=0·03).

512 adverse events were reported by 92 participants by the end of the open-label period. 378 of these adverse events were related to study devices or implantation (table 4; appendix pp 8–9). Most of the related adverse events were associated with surgery (appendix p 9). 317 of the 378 related adverse events occurred within 30 days of implantation. The most common related adverse events occurring within 30 days of implantation were numbness, pain, swelling, headache, paraesthesias, bruising, trismus, tenderness, taste alterations, and restricted jaw movement (table 4). The most common related adverse events from 30 days after implantation to the end of the follow-up period were unpleasant sensations with stimulation, headache, and pain (appendix p 9).

Nine serious adverse events were reported in nine patients, all of which completely resolved. Three were related to the implantation procedure (aspiration during intubation, nausea and vomiting, and venous injury or compromise), and one was related to both the device and the procedure (infection). All related serious adverse events except for the infection occurred within 30 days of surgery. The case of infection occurred 31 days after surgery and resolved within 1 year of implantation. The other five serious adverse events were judged not to be related to study devices or procedures. There were no unanticipated serious adverse events.

There were two explantations by the end of the open-label phase: one 35 days after implantation because of infection, and one 98 days after implantation, which was done to reposition the neurostimulator (ie, reimplantation). Lead revision occurred in one patient 274 days after implantation.

	Sphenopalatine ganglion stimulation group	Control group	Odds ratio (95% CI)	p value
Pain relief at 15 min				
50% response	15/24 (63%)	8/28 (29%)	4·04 (1·13–15·73)	0·03
75% response	11/24 (46%)	3/28 (11%)	6·72 (1·44–44·50)	0·01
100% response	4/24 (17%)	1/28 (4%)	5·24 (0·47–275·56)	0·26
Freedom from pain at 15 min				
50% response	9/24 (38%)	3/28 (11%)	4·84 (1·00–32·20)	0·049
75% response	5/24 (21%)	1/28 (4%)	6·86 (0·69–348·20)	0·13
100% response	1/24 (4%)	1/28 (4%)	1·17 (0·01–95·52)	1·00
Sustained pain relief at 1 h				
50% response	13/23 (57%)	3/28 (11%)	10·26 (2·19–68·28)	0·001
75% response	6/23 26%)	2/28 (7%)	4·45 (0·69–50·14)	0·14
100% response	1/23 (4%)	1/28 (4%)	1·22 (0·02–99·86)	1·00
Weekly attack frequency				
50% response	28/45 (62%)	25/45 (56%)	1·31 (0·52–3·33)	0·67
75% response	22/45 (49%)	11/45 (24%)	2·92 (1·11–8·07)	0·03
100% response	7/45 (16%)	4/45 (9%)	1·88 (0·44–9·45)	0·52

Data are n/N (%).

Table 3: **Patient-level efficacy outcomes**

Discussion

In this randomised, double-blind, sham-controlled, parallel group study, we showed that sphenopalatine ganglion stimulation in patients with chronic cluster headache relieved acute attacks within 15 min significantly more often than sham stimulation. Ancillary analyses provided some evidence that more patients had pain relief and freedom from pain at 15 min and sustained pain relief at 1 h after at least 50% of attacks with sphenopalatine ganglion stimulation than with sham treatment. Although this trial was not designed as a preventive study, post-hoc analyses provided weak evidence showing that more patients in the sphenopalatine ganglion stimulation group than in the control group seemed to have a reduction in the mean weekly frequency of ipsilateral cluster headaches of at least 75%. Overall, adverse events were consistent with safety data from the previous study,[22] and, in line with other experience,[26] we recorded no unexpected serious adverse events. The device was generally well tolerated. These findings, together with those of the previous study,[22] suggest that sphenopalatine ganglion stimulation could be a potential therapeutic option for chronic cluster headache.

The sphenopalatine ganglion is the main outflow pathway for the cranial parasympathetic system.[16] Stimulation of the trigeminal ganglion in humans beings[30,31] can lead to activation of a trigeminovascular pathway. Furthermore, in laboratory bench work, this pathway predominantly acted through the ophthalmic division of the trigeminal nerve[32] and had relative somatotopic and functional fidelity.[33] The outflow pathway for the trigeminal–autonomic reflex involves the superior salivatory nucleus in the pons,[34] traverses the facial (VIIth) cranial nerve,[32] and synapses in the sphenopalatine ganglion[35] with a classic nicotinic autonomic ganglion receptor mechanism,[17,36] ultimately releasing vasoactive intestinal polypeptide[37] and probably other related neuropeptides, such as pituitary adenylate cyclase activating peptide[38] and helospectin-like peptides.[39] The cranial parasympathetic outflow pathway explains the clinical symptoms so prominent in trigeminal autonomic cephalagias—eg, lacrimation, conjunctival injection, nasal and aural symptoms—through direction activation.[1,40] Sympatholytic symptoms, such as ptosis and miosis, are

	Sphenopalatine ganglion stimulation group (n=45)	Control group (n=48)
Allergic reaction	1 (2%)	0
Bleeding	3 (7%)	0
Bruising	4 (9%)	9 (19%)
Device movement	1 (2%)	0
Dizziness	1 (2%)	0
Dysaesthesias (transient or permanent)	1 (2%)	2 (4%)
Epistaxis	2 (4%)	0
Headache	10 (22%)	11* (23%)
Hypoaesthesias (transient or permanent)	2 (4%)	0
Infection	1 (2%)	2 (4%)
Restricted jaw movement	3 (7%)	2 (4%)
Maxillary sinus penetration	1 (2%)	0
Numbness (transient or permanent)	30 (67%)	36 (75%)
Other	16† (36%)	21‡ (44%)
Pain	19§ (42%)	22¶ (46%)
Paraeasthesias (transient or permanent)	7 (16%)	9 (19%)
Reduction in tearing	2 (4%)	2 (4%)
Rhinorrhoea	0	1 (2%)
Sensations while chewing or talking	1 (2%)	0
Swelling	16 (36%)‖	23** (48%)
Taste alterations	3 (7%)	3 (6%)
Tearing	0	2 (4%)
Tenderness	5 (11%)	3 (6%)
Toothache, tooth decay, tooth loss, or tooth extraction	0	1 (2%)
Trismus	4 (9%)	6 (13%)
Venous injury or compromise	0	1 (2%)
Visual disturbances	0	2 (4%)
Xerophthalmia (dry eye)	1 (2%)	0

Adverse events were classed as related to the device implanted or the implantation procedure if they were possibly, probably, or highly probably related. This table includes related serious adverse events. *12 events in 11 patients. †24 events in 16 patients. ‡31 events in 21 patients. §20 events in 19 patients. ¶25 events in 22 patients. ‖16 events in 17 patients. **24 events in 23 patients.

Table 4: **Specific device-related or implantation-related adverse events from implantation to day 30**

probably due to a third-order neuron effect on the carotid sympathetic plexus.[41] The sphenopalatine ganglion provides a physiological link between trigeminal pain and the cranial autonomic features typical of trigeminal autonomic cephalagias, and thus has been a potential target for treatments.

In patients probably with migraine with cranial autonomic features, Sluder[41] applied one drop of a 20% cocaine solution to the region of the sphenopalatine ganglion and found this to be clinically useful. Various other therapeutic interventions have been tried, including surgical interruption,[42] stereotactic gamma knife,[43] electrolytic lesion,[20] onabotulinumtoxinA,[44] and local anaesthetic blockade.[45] Electrical stimulation of the sphenopalatine ganglion was used acutely to treat cluster headache and was reported to be successful.[21] On the basis of the clear basic science anatomy, physiology, and results from therapeutic intervention directed towards the sphenopalatine ganglion in human studies, an implantable sphenopalatine ganglion stimulator was developed and tested in chronic cluster headache.[22] 28 patients completed a crossover study in which a random insertion of sham was also used. Device stimulation was more effective than sham for the relief of acute cluster headaches, and one-third of patients had a reduction in attack frequency,[22] which for many persisted for at least 2 years.[46] An important limitation of that study was that an appropriate sham therapy was not used.[23] In this study, we used an appropriate sham to establish the sphenopalatine ganglion as a target for therapy in chronic cluster headache.

In neuromodulation studies, blinding is perhaps the greatest issue for trial design.[23] We used a sham control that consisted of cutaneous electrical stimulation, which could be felt by patients. This approach overcame an important obstacle in this field. However, similar to non-invasive vagal nerve stimulation for treatment of acute cluster headache,[10,11] in which a low level of stimulation is used, there was clear differentiation between active stimulation and sham in terms of clinical outcome, with a similar cutaneous sensation. Another limitation in our study was the implantation effect: some patients had no further attacks after implantation for at least a year (data not shown)—a delay far longer than would be expected as a result of simple manipulation effects, which are regularly noted in neuromodulation studies. Furthermore, it seems possible that the implantation effect is not limited to the initial period, such that some of the reduction in attack frequency noted in the sham group could be due to the same mechanism. Disentangling these effects is very difficult in a clinical trial. However, for patients with chronic cluster headache, who have very few effective and well tolerated treatment options, the possibility of remission for at least a year after the procedure is not a practical disadvantage.

From a mechanistic viewpoint, there is a question as to whether the study intervention blocks or stimulates the sphenopalatine. Low-frequency stimulation—ie, 5 Hz—could trigger attacks, whereas high-frequency stimulation with 120 Hz, as used in our study, does not seem to.[47] This finding is in line with what is known about the physiology of this outflow pathway.[48]

Neuromodulation approaches are costly compared with drug approaches. However, our participants were patients in whom previous medical treatments were unsuccessful, so to some extent the question is moot. A European registry study[49] showed a 50% reduction in acute treatment costs and a 40% reduction in preventive treatment costs when sphenopalatine ganglion stimulation was used over

a 1-year period. Similarly, on the basis of data from the Pathway CH-1 study,[22] meaningful gains in quality of life could be expected from sphenopalatine ganglion stimulation in patients with chronic cluster headache.[50] Given that positive results persist in most patients for up to 2 years,[46] it seems probable that sphenopalatine ganglion stimulation will prove cost effective in the median term. Further data on the use of, and clinical experience with, sphenopalatine ganglion stimulation will allow elaboration of the role of this therapy in chronic cluster headache.

Contributors

PJG and DWD designed the study, reviewed patients for inclusion in the trial, and advised on data analysis and interpretation. SS-S, EJK, AHC, DCM, PJM, PDC, DIF, JRZ, LLM, SRP, and ARR had roles in study execution and data interpretation. PJG and DWD wrote the first draft of the Article, which was reviewed and approved by all other authors.

Declaration of interests

PJG reports grants and personal fees from Amgen and Eli-Lilly; personal fees from Autonomic Technologies, Alder Biopharmaceuticals, Allergan, Biohaven Pharmaceuticals, Dr Reddy's Laboratories, Electrocore, eNeura, Impel NeuroPharma, MundiPharma, Novartis, Teva, WL Gore, and Trigemina; and fees for publishing from Oxford University Press, Massachusetts Medical Society, and Wolters Kluwer. He holds stock options in Trigemina, and has received fees for medicolegal work. PJG also holds a patent for magnetic stimulation for headache, which is licensed to eNeura without fee. SS-S has received speaker fees from Allergan and Depomed. AHC reports speaker fees from Amgen, Avanir, and Depomed, and is a consultant for Eli Lilly. PJM reports grants from Autonomic Technologies, and grants and personal fees from Electrocore, Amgen, Allergan, Teva, and Eli Lilly. DIF reports grants from Autonomic Technologies, Merck, and Zosano; personal fees from Allergan, Avanir, Supernus, Teva, Biohaven Pharmaceuticals, Amgen, and Alder Biopharmaceuticals; and grants and personal fees from Eli Lilly and electroCore. ARR reports personal fees from and an equity position with Autonomic Technologies, and equity positions with Neurotechnology Innovation Translator, Neurotechnology Innovation Management, and Sollis Therapeutics. ARR also holds a patent for Autonomic Technologies. DWD reports personal fees from Acorda, Amgen, Alder, Allergan, Autonomic Technologies, Biohaven, Colucid, Eli Lilly, eNeura, Foresight, Zosano, WL Gore, Vedanta Associates, Promius Pharma, Magellan Healthcare, CC West Ford Group, Nocira, Novartis, NuPathe, Supernus, Electrocore, Tonix, Alcobra, Insys, Ipsen, Charleston Laboratories, Biocentric, Theranica, Xenon, and ZP Opco; personal fees and travel expenses from Sun Pharma; speaker fees or fees related to content development for continuing medical education from Healthlogix, Medicom Worldwide, Medlogix Communications, MedNet, Miller Medical Communications, PeerView Operation Services America, Web MD/Medscape, the American Academy of Neurology, the American Headache Society, PeerView Institute for Medical Education, Chameleon Communications, the Academy for Continued Healthcare Learning, Universal Meeting Management, Haymarket Medical Education, Global Scientific Communications, UpToDate, and Meeting LogiX; royalties for editorial work or book publishing from Oxford University Press, Cambridge University Press, Wiley Blackwell, Sage, and Wolters Kluwer. He has chaired a data safety monitoring committee chair for Axsome; has a consulting use agreement through his employer with NeuroAssessment Systems and Myndshft; holds equity in Healint, Theranica, Second Opinion/Mobile Health, and Epien; and is on the board of directors of King-Devick Technologies and Ontologics. EJK, JRZ, LLM, and SRP report grants from Autonomic Technologies. DCM and PDC declare no competing interests.

Data sharing

The data reported here are proprietary to the sponsor, Autonomic Technologies, and there are no plans to make the individual patient data or aggregate data publicly available.

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