ORIGINAL ARTICLE

Cervical 10 kHz spinal cord stimulation in the management of chronic, medically refractory migraine: A prospective, open-label, exploratory study

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Abstract

Background: A significant minority of chronic migraine (CM) subjects fail conventional medical treatment (rCM), becoming highly disabled. Implantation of an occipital nerve stimulator is a therapeutic option for these subjects. Paresthesia-free cervical 10 kHz spinal cord stimulation (HF10 SCS) may provide an alternative. We report the results of a prospective, open-label, exploratory study assessing the long-term safety, tolerability and efficacy of cervical HF10 SCS in cohort of rCM subjects.
Methods: Included subjects were diagnosed with CM by an experienced headache specialist with the aid of an hourly headache diary. They were refractory to conventional medical treatments including onabotulinumtoxin-A injections. Medication overuse headache was not an exclusion criteria. Enrolled subjects underwent a 2- to 4-week tunnelled cervical HF10 SCS trial followed by a permanent system implant if a significant, subjective reduction in headache intensity/episodes was reported during the trial. Subjects were evaluated at baseline and 6 months after implantation with the aid of monthly diaries and headache-specific questionnaires.
Results: Seventeen subjects underwent a trial of cervical HF10 SCS; 14 were still implanted at 6 months (one trial failure, one trial infection, one implant site infection). Seven of the 14 subjects had >30% reduction in headache days. The average reduction in headache days was 6.9 for the overall population and 12.9 among the responders. Three subjects reported tenderness over the IPG/connection site, and one had a lead migration that required surgical revision.
Conclusion: Paresthesia-free cervical HF10 SCS may be a safe and effective therapeutic option for chronic migraineurs refractory to conventional treatments.

1. Introduction

Chronic migraine (CM) is diagnosed when subjects report at least 15 days of headache per month, with at least 8 of these days fulfilling the criteria for migraine headache (Headache Classification Subcommittee of the International Headache Society, 2004). CM is a severely debilitating condition affecting 2–5% of the adult population (Irimia et al., 2011; Lipton, 2011). Refractory chronic migraine (rCM) is diagnosed when subjects continue to suffer with CM despite adequate

trials of prophylactic and acute medications with proven efficacy (Schulman et al., 2008).

CM is currently considered as a disorder of the central nervous system (Goadsby and Sprenger, 2010) that leads to structural, functional and pharmacological changes in the brain of affected subjects (Mathew, 2011). Occipital nerve stimulation (ONS) for refractory CM takes advantage of the functional continuum of the trigeminal nucleus into the dorsal horn of the high cervical region to neuromodulate, in a retrograde fashion, the trigeminocervical complex (Bartsch and Goadsby, 2003; Goadsby et al., 2009; Ellens and Levy, 2011). Case series show occipital nerve stimulation to be efficacious for the treatment of several headache disorders including migraine headaches, cluster headache, hemicrania continua and occipital neuralgia (Ellens and Levy, 2011). Large, multi-centre, randomized studies in refractory CM have shown efficacy – but the effect was less dramatic than expected (Goadsby and Sprenger, 2010; Ellens and Levy, 2011).

HF10 SCS has been shown to be effective in some chronic pain conditions and has the advantage to be paresthesia-free (Al-Kaisy et al., 2014, 2015; Van Buyten et al., 2013). It is reasonable to postulate that cervical HF10 SCS may also neuromodulate the trigeminocervical complex and thus have an effect on chronic rCM as traditional, low-frequency stimulation of the cervical spinal cord has shown positive results in a series of chronic cluster headache subjects (Wolter et al., 2011).

The aim of this prospective, open-label, exploratory study was to assess short and long-term safety, tolerability and efficacy of cervical HF10 SCS in subjects suffering from chronic migraine refractory to conventional medical therapy.

2. Methods

This was a prospective, open-label, exploratory study to assess the feasibility of cervical HF10 SCS as a treatment for subjects with rCM. The study received local ethics committee approval (Protocol Code Number CE100112) and was registered on clinical trials databases (NCT01653340 and EudraCT 2012-002005-22). All subjects provided written informed consent.

2.1. Participants

Subjects aged 18–65 suffering from rCM were screened by an experienced headache specialist who confirmed the diagnosis of CM according to the guidelines published by the International Headache Society (ICHD II) with the aid of a 30-day subjects' headache hourly diary (Headache Classification Subcommittee of the International Headache Society, 2004).

The diagnosis of rCM was confirmed using the criteria provided by the Refractory Headache Special Interest Section of the American Headache Society (Schulman et al., 2008) – subjects had failed adequate trials of at least two preventive drugs (among the following classes: beta blockers, anticonvulsants, tricyclics, calcium channel blockers), and abortive medicines (both a triptan and a non-steroidal anti-inflammatory drug or combination analgesic).

Subjects fulfilling inclusion/exclusion criteria (Table 1) completed a 30-day headache diary (which also served as their baseline for the study) and those subjects with at least 15 headache days per diary were considered eligible for the study.

Diaries of eligible subjects were carefully evaluated for medication overuse (MO) according to the ICDH-II criteria (Silberstein et al., 2005). MO was not an exclusion criteria, provided that subjects were on stable dose of medication for at least 6 months. Subjects were allowed to continue their usual medications, including stable doses of migraine preventive drugs.

2.2. Study design

Recruited subjects received a 'tunnelled' trial of cervical HF10 SCS for 2–4 weeks to assess tolerability to the treatment. Because this was an exploratory study, we did not set a pre-specified threshold to classify subjects as responders at the end of the trial phase. The decision to proceed to the permanent implant of the system was left to the recruited subjects, who were advised to take into consideration

Table 1 Inclusion and exclusion study criteria.

Inclusion criteria	Exclusion criteria

Diagnosis of:
• Migraine
   (ICDH-II criteria)
• Chronic
   (>15 headache days[a] per month)
• Refractory
   (not responsive or intolerant to 2 preventive
   and 2 abortive drugs)
On stable medications for at least 2 months
Failed treatment (for at least 12 months) with
   Onabotulinumtoxin-A
Able to comply with the requirements of the study
   visits and questionnaires
	Treatment with onabotulinumtoxin-A in the last 3 months
	Previous surgery at cervical spine, trigeminal or sphenopalatine level
	Arnold–Chiari malformation
	Pregnancy or potential for with unwillingness to use contraception
	Fibromyalgia or other widespread chronic pain
	Presence of an implanted electrical device
	The need or the expected need for MRI scans
	Significant psychiatric illness, severe depression and/or addictive behaviour
	Unresolved litigation
	Unavailability for appropriate follow-up throughout the whole duration of study

[a]Please see the Method section for the definition of headache day.

changes in headache intensity, severity, frequency and abortive medication dosage together with any stimulation-related side effects.

2.3. Procedures

Epidural lead placement was performed through a small skin incision under local anaesthesia supplemented by conscious sedation. Under fluoroscopic control, a 15-gauge Tuohy type needle was introduced at the upper thoracic level and advanced into the epidural space using a 'loss of resistance' technique. One or two-eight-contact cylindrical leads were advanced cranially in the posterior epidural space under continuous fluoroscopic control, until the distal tip was at the C_2 vertebral level (Fig. 1). The leads were anchored and sutured to the supra-spinal fascia, connected to temporary extensions, tunnelled 20–30 cm under the patient's skin and connected to a temporary external stimulator for the duration of the trial period. Stimulation programmes (10 kHz, 30 μs) were provided to target the dorsal columns in the area corresponding to C_2–C_3 vertebral level. A sensory threshold for each programme was determined (up to a max amplitude value of 4 mA), and stimulation was initially set to 50% of that value, with the patient able to adjust it within a 10–70% range.

At the end of the trial period, subjects choosing to receive the permanent system implantation returned to the operating room. The proximal end of the tunnelled lead(s) were connected to new sterile extensions which provided connection to the pulse generator (Senza™ system, Nevro Corp., Menlo Park, USA), which was implanted either in the anterior abdominal wall or the gluteal region. Perioperative antibiotic coverage was administered at both trial and permanent implant stages.

2.4. Data collection and outcome measures

Subjects were asked to complete a month-long (30 day) hourly diary before assessment (Baseline) and every month after the implant until the end of the 6-month study period.

Adverse events were recorded as a measure of treatment safety and tolerability (Table 2). More specifically, data regarding lead migration, lead fracture, lead disconnection, current leakage, need for battery replacement, early- and late-onset infections, skin erosion, system-induced muscle spasms, painful IPG pocket and any new neurological symptoms were systematically collected and reported.

As this was an exploratory study, no primary endpoint was defined. However, a range of efficacy mea-

Figure 1 Antero-posterior and lateral radiographic view of the cervical spine to demonstrate the final position of the implanted leads within the posterior epidural space.

sures was prospectively collected and evaluated at each follow-up including frequency of headaches (expressed as number of headache days in a 30-day period), the intensity and the length of the headaches (for a 30-day period expressed as the average of the mean NRS per day, and the cumulative hours of headache, respectively). A headache day was defined as calendar day with at least 4 h of continuous headache with a NRS >4, or with any NRS if concomitant with the intake of triptans or ergotamine (Silberstein et al., 2008).

The change from baseline in headache days, headache duration and/or intensity prior to a schedule follow-up, and the proportion of subjects who reported at least 30% and 50% reduction in headache days (30% and 50% responders, respectively) were examined as efficacy measures.

Headache-specific questionnaires were administered at baseline and at each scheduled follow-up, and stimulation-induced score reductions for each questionnaire were considered as an additional efficacy measure. The Headache Impact Test (HIT-6) and the Migraine Disability Assessment Scale (MIDAS) were used to assess the headaches impact and interference on subjects' function and quality of life (Yang et al., 2011; Bagley et al., 2012). The use of more than one questionnaire has been shown to give a more accurate

assessment of patient's headache-related disability (Sauro et al., 2010).

The short-form SF-12 questionnaire was chosen as measure of health-related quality of life in two main domains, a physical (PCS-12) and a mental (MCS-12) component (Ware et al., 1996).

2.5. Statistical analysis

Descriptive statistics were reported as counts and percentages, mean and standard deviation or median and range. Adverse events (AEs) were reported descriptively. Data from the subjects' diaries were adjusted for a 30-day month length when necessary. Differences from baselines were compared for continuous variables, using the independent sample Student's t-test or Wilcoxon–Mann–Whitney test and, for dichotomous variables, using the χ^2 test or Fisher's exact test, as appropriate.

This was a 'hypothesis-generating' feasibility study; therefore, no sample size was formally determined.

3. Results

Between June 2012 and July 2013, 47 subjects with a diagnosis of rCM were screened for the study and 17 of those underwent a trial of HF10 SCS. Fifteen subjects decided to receive a permanent implant, and 14 were available for the 24 weeks of follow-up. The study flow chart is available online (Figure S1), while characteristics of the enrolled subjects and studied population are given in Table S1 and Table S2, respectively. None of the participants used any prophylactic drugs within the 4 weeks prior the inclusion or during the 24-week study protocol.

3.1. Feasibility and safety

All enrolled subjects tolerated the treatment; there were no reports of serious, unanticipated adverse device effects. Table 2 summarize the AEs monitored at each follow/up visit. None of the subjects reported any paresthesia sensation while the device was providing HF10-SCS epidural stimulation, one subject reported small areas of cutaneous hypoesthesia which resolved with device re-programming. Six adverse events classified as severe occurred in five subjects. Four AEs were considered hardware or procedure-related and required surgical treatment (one IPG removal for pocket infection, one trial lead removal for wound infection, one lead repositioning due to migration and high impedances in the top lead contacts). Two additional subjects reported dis-

Table 2 Adverse events: definition and incidence.

Adverse events	N	Severity	SAE
Device-related			
Lead migration	2 (1)[a]	Severe[a]	Yes
Lead fracture	1 (1)[a]	Severe[a]	Yes
Lead disconnection	0	–	–
Current leakage	0	–	–
Battery depletion	0	–	–
Early (trial) system infection	1 (1)	Severe	Yes
Late-onset system infection	1 (1)	Severe	Yes
Skin erosion	0	–	–
System-induced muscle spasm	0	–	–
Discomfort at the implant site	2	Mild	No
Pain and Oedema at pulse generator site	1	Moderate	No
Onset of new neurological symptoms	0	–	–
Hypoesthesia (Shoulder area)	1	Moderate	No
Shoulder pain	1 (1)[b]	Moderate	Yes
Device unrelated event			
Myocardial infarction	1	Severe	Yes
Transient ischaemic attack	1	Severe	No
Total	12 (4)	Severe: 6	6

Number in brackets indicates how many subjects required revision surgery to address the corresponding AE; SAE, serious adverse event.
[a]Occurred in the same subject.
[b]Ongoing.

comfort at the IPG implant site, but they did not require any medical or surgical treatment. Radiographic lead migration was documented in two implanted subjects, one of which required surgery to reposition the lead.

3.2. Headache days

Compared with the baseline period, the average reduction in headache days observed at 24 weeks was 7.0 days (95% CI: 2.7–11.3) ($p = 0.004$ paired t-test). Seven (50%) subjects recorded a >30% decrease in headache days (average reduction: 12.9 ± 5.3 days), while 5 (36%) subjects reported a reduction in headache days greater than 50% (average reduction: 14.8 ± 4.9 days) at 24 weeks. Eight subjects (57%) reverted to an episodic pattern of headache (<15 days a month).

3.3. Other (secondary) outcomes

3.3.1. Medication intake

All subjects were overusing medication prior to enrolment: 64% were using triptans for more than 9 days per month and 36% were using other analgesics (NSAIDs, opioids, caffeine, paracetamol) for more than 14 days per month. At 24 weeks follow-up, subjects (ab)using of triptans or NSAIDS were, respectively 36% and 14%; four subjects discontinued the use of triptans.

3.3.2. Questionnaires

MIDAS and HIT-6 scores decreased significantly at 24 weeks follow-up compared to baseline values, respectively by 115 (95% CI: 76–154, $p < 0.001$, paired t-test) and 8.3 (95% CI: 3.0–13.6, $p < 0.01$, paired t-test) points. At baseline, 100% of subjects were classified as severely disabled according to both scales, while at 24 weeks, the percentage severely disabled dropped to 69% (MIDAS) and 62% (HIT-6) (Fig. 2). Compared with baseline values, the physical component of the SF-12 questionnaire at 6 months showed a significant improvement of 7.6 points (95% CI: 0.8–14.5, $p = 0.046$, paired t-test), while the mental component did not significantly change.

3.3.3. Intensity and frequency of headaches

The average headache intensity and frequency (number of headache hours) decreased significantly at 3 months (respectively, 49% and 40% reduction, $p < 0.001$ and $p = 0.013$ vs. baseline, paired t-test)
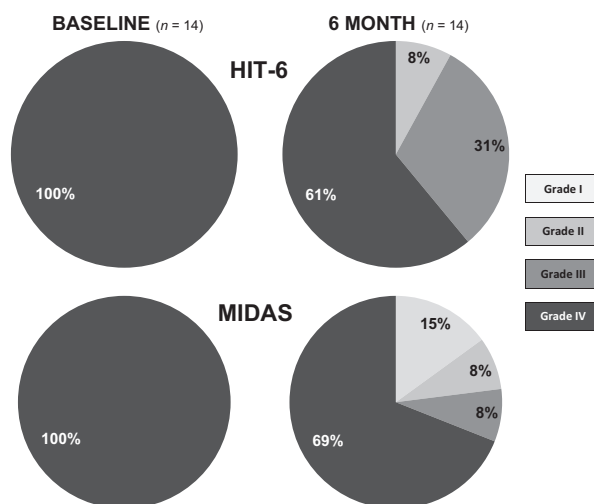

Figure 2 Six-month HF10 SCS effect on headache-specific disability questionnaires. 31% (MIDAS) and 39% (HIT-6) of the subjects initially scoring within the highest disability range moved into a lower class after 6 months of HF10 SCS treatment.

and at 6 months (respectively, 37% and 17% reduction, $p < 0.001$ and $p = 0.05$ vs. baseline, paired t-test). Half of the subjects reported more than 30% reduction in headache intensity at 6 months (average reduction 3.3 ± 1.2 points), while 43% reported more than 30% reduction in the monthly hours of headache (average reduction 92 ± 41 h). Fig. 2 shows the average intensity and length of the headache in the studied population per each day of the month both at baseline and at 6 month.

3.3.4. Sleep

The average sleep hours increase (from an average of 6.9 per day to 7.4 h) was not statistically significant.

4. Discussion

Migraine is the leading cause of disability among neurological disorders, and globally ranks 7th among all specific causes of disability (Vos et al., 2012). Subjects suffering from rCM represent a significant medical challenge (Schulman et al., 2009; Martelletti et al., 2014). Consideration of invasive, surgical options is justified in the context of this severely disabling medical condition that poses a substantial burden on subjects' quality of life and on health services utilization.

Occipital nerve stimulation is currently the treatment of choice in selected cases of rCM, as it is relatively safe and has evidence of efficacy (Goadsby

et al., 2009; Ellens and Levy, 2011; Martelletti et al., 2013). However, larger studies designed to better define the efficacy of ONS in CM have proved disappointing as over-ambitious endpoints have been missed (Silberstein et al., 2012). This, together with a significant incidence of hardware-related adverse events (lead migration, lead fracture, skin erosion, pain and discomfort), has limited the use of ONS systems. Many of the ONS complications are related to the obligatory siting of the leads subcutaneously in the highly mobile cervico-cranial junction area. This results in more complications than seen with spinal cord stimulation systems where the leads are implanted deeper (within the spinal canal), more axially, and are therefore subjected to less movement.

HF10 SCS is a paraesthesia-free system which has been shown to inhibit evoked afferent nociceptive inputs by modulating wide-dynamic range neuronal activity in the spinal cord of different animal models (Cuellar et al., 2013). It has shown remarkable clinical efficacy in human refractory back pain (Al-Kaisy et al., 2014; Van Buyten et al., 2013) and, when applied to the cervical epidural space, it has been also reported as safe and effective in a series of subjects with upper limb neuropathic pain (Al-Kaisy et al., 2015). It is reasonable to postulate that HF10 SCS may also modulate the trigeminocervical complex and thus have an effect on chronic rCM.

The results of our study are promising – half of the subjects reported a >30% reduction in headache days, 36% reported a reduction greater than 50%, and eight subjects reverted to an episodic migraine pattern; similarly, both the MIDAS and HIT-6 questionnaires showed a significant decrease in the headaches impact and interference on subjects' function and quality of life. Medication intake reduced significantly, and four subjects discontinued triptans use at 6-month follow-up.

At first glance, these results seem similar to those reported for ONS (Saper et al., 2011; Silberstein et al., 2012). However, there are some significant differences between this trial and the published ONS studies. Firstly, the ONS studies included only subjects with a predominant occipital pain distribution. This does not reflect the overall migraine population. When a very large cohort of headache subjects was studied to characterize their headache locations, only 40% of migraneurs reported occipital pain, while the anterior location of the head was the commonest site for headache (Kelman, 2005; Barmettler et al., 2014). The headache popul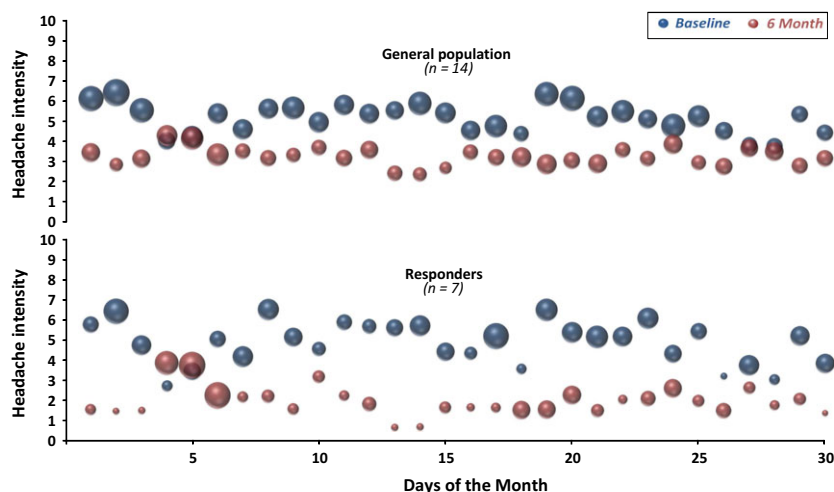ation recruited in our study was *not* been selected by headache topography (see Table S1). Secondly, in addition to failing conventional medication therapy, this study included only subjects who had failed to benefit from onabotulinumtoxin-A therapy. The ONS studies lack this additional refractory criteria. Onabotulinumtoxin-A is a safe and effective treatment in many otherwise rCM subjects, and a recent consensus statement from the European Headache Federation advocates its addition to the preventive treatment list to be tried before labelling a migraine patient as refractory (Martelletti et al., 2014).

Neuromodulation is an expensive and invasive treatment, with a risk of device-related adverse events. It should be reserved for subjects refractory to other effective treatments and subjects should undergo careful psychological assessment prior to proceeding with a trial. Recommendations for SCS patient selection have always included psychological evaluation, which is designed to help identify an ideal patient to achieve maximum benefit from an implanted device (Celestin et al., 2009). In our study, 28% of the eligible subjects were excluded after being deemed psychologically unsuitable for a long-term implanted device. Available evidence suggests that pre-surgical psychological factors including somatization, depression, anxiety and poor coping are predictive of poor response to spinal cord stimulation (Celestin et al., 2009).

Serious concerns have been expressed about the high complication rates of peripheral nerve stimulation techniques when used in CM subjects (Mueller et al., 2013). In the only large-scale, prospective, controlled study evaluating ONS for CM with 1-year follow-up to date, the safety profile of the therapy was questioned by the authors themselves, as 183 device- or procedure-related AEs occurred, 8.6% of which required hospitalization and almost 41% required additional surgery (Dodick et al., 2014). During our exploratory study, 12 AEs occurred (see Table 2), with four subjects (24%) needing an additional surgical procedure. This lower complication rate could be due to the small size of our study, but, as stated before, might also be attributed to the epidural, axial placement of HF10-SCS leads, which could result in fewer complications than the peripheral placement of ONS leads at the mobile craniocervical junction.

A successful temporary trial of stimulation has been considered the best predictor of long-term outcome in different groups of chronic pain subjects who are candidates for neuromodulation (Barolat et al., 1998). We have previously questioned the role of a stimulation trial when treating CM migraine

Figure 3 Average intensity and length of the headache episodes in the studied population. The average daily headache data of the studied population are plotted using the figures from the 30-day subjects' hourly diaries. Each 'bubble' is proportional to the average intensity ('height' of the bubble on the x-axis) and the average length ('width' of the bubble) of the headache episode. The upper panel shows data from the whole populations, the lower panel from only those subjects who report a >30% reduction in headache days (responders, n = 7).

subjects, as its ability to select long-term responders appears poor. With a very high percentage (>80%) of subjects going on to full implantation, a trial poses additional risk and inconvenience for subjects and an economic burden to the health care system (Palmisani et al., 2013). The results of this study support this impression. We included a stimulation trial phase in the study design to assess tolerability to the treatment, but we left the decision to proceed to permanent implant to the recruited subjects. We are aware that this is not standard practice in neuro-modulation, but the exploratory nature of this study justifies our choice of not pre-define any objective outcome to define trial success. All subjects tolerated the treatment, and only one of the 17 trialled subjects did not report significant improvement in the headaches. One of the two infections that occurred during the study was an early trial wound colonization with subsequent subcutaneous abscess, and this may have been avoided with either a no-trial policy or with a short 3–7-day percutaneous trial.

We followed the latest guidelines on controlled trials of prophylactic treatment of CM in adults (Silberstein et al., 2008), calculating outcome measures from the data collected with the aid of a prospective headache diary. This may be a study weakness. Paper–pencil diaries are associated with drawbacks including low compliance and backfilling diary entries (Stone et al., 2002). Existing guidelines have not produced a standardized version of a headache diary. This may lead to discrepancies when comparing results from different studies where different diaries are used. We opted for an hourly headache intensity diary, which we believe allowed a more precise and accurate evaluation of headaches length and intensity (see Fig. 3), together with a generic

recording of medication intake. However, this type of diary did not record any autonomic symptoms associated with the headache, and was not able to clearly discriminate the exact relationship between the taking of triptans/ergot and headache resolution.

The study results at 24 weeks of treatment indicate that cervical HF10 SCS has promise as a treatment for rCM. HF10 SCS appears to have efficacy, be relatively safe, and be well tolerated in subjects with rCM. The significant reduction in the number of headache days in the studied population at 6 months, the relative high number of 'responders' and the substantial decrease in the headache-specific questionnaires scores compares favourably to results seen in studies with ONS, and should encourage further clinical investigations to evaluate a possible role of HF10 SCS in the management of rCM.

Author contributions

SP, RA, PM, TS and AA substantially contributed to the conception and design of the study. RA, SP, VV, ST, MRDF and MM were significantly involved in the acquisition of data, analysis and interpretation of data. SP, TS and RA drafted the first version of the article. All authors provided significant intellectual contribution and approved the final version of the manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. Study flow chart.

Table S1. Enrolled subjects: demographics and headache phenotype.

Table S2. Study population: demographics and baseline characteristics.