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ORIGINAL

Safety and efficacy of deep brain stimulation in refractory cluster headache: a randomized placebo-controlled double-blind trial followed by a 1-year open extension

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Abstract Chronic cluster headache (CCH) is a disabling primary headache, considering the severity and frequency of pain attacks. Deep brain stimulation (DBS) has been used to treat severe refractory CCH, but assessment of its efficacy has been limited to open studies. We performed a prospective crossover, double-blind, multicenter study assessing the efficacy and safety of unilateral hypothalamic DBS in 11 patients with severe refractory CCH. The randomized phase compared active and sham stimulation during 1-month periods, and was followed by a 1-year open phase. The severity of CCH was assessed by the weekly attacks frequency (primary outcome), pain intensity, sumatriptan injections, emotional impact (HAD) and quality of life (SF12). Tolerance was assessed by active surveillance of behavior, homeostatic and hormonal functions. During the randomized phase, no significant change in primary and secondary outcome measures was observed between active and sham stimulation. At the end of the open phase, 6/11 responded to the chronic stimulation (weekly frequency of attacks decrease >50%), including three pain-free patients. There were three serious adverse events, including subcutaneous infection, transient loss of consciousness and micturition syncopes. No significant change in hormonal functions or electrolytic balance was observed. Randomized phase findings of this study did not support the efficacy of DBS in refractory CCH, but open

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phase findings suggested long-term efficacy in more than 50% patients, confirming previous data, without high morbidity. Discrepancy between these findings justifies additional controlled studies (clinicaltrials.gov number NCT00662935).

Keywords Cluster headache · Deep brain stimulation · Hypothalamus · Headache · Pain modulation · Randomized trial

Introduction

Cluster headache (CH) is a primary headache and belongs to the group of the trigeminal autonomic cephalalgias in the International Classification of the Headaches Disorders [1–3]. CH mainly affects men and is characterized by strictly unilateral short-lasting pain attacks associated with prominent parasympathetic features. Episodic CH affects 80–90% of patients who describe periods of attacks (cluster) and periods of remission. Chronic CH (unremitting from onset or evolved from episodic form) lacks the remissions and is diagnosed after 1 year without remission or with remission periods lasting less than 1 month [2]. CH is one of the most painful conditions in humans and is often referred to as "suicidal headache". The pathophysiology of CH revolves around the trigeminal-autonomic reflex whose activation explains the trigeminal topography of pain and the ipsilateral autonomic features [4]. Functional imaging demonstrated a brain activation during attacks [5], co-localized with a structural change, in the posterior hypothalamic region. [6]. This prompted the use of deep-brain stimulation (DBS) to modulate this region in a patient with refractory chronic CH which led to complete relief from attacks [7]. Based on this observation, DBS was introduced in the treatment of medically refractory chronic CH. After 8 years of experience, DBS is claimed to be successful in controlling the pain attacks in about 60% of the 41 chronic CH patients implanted worldwide [8–14]. Yet such a claim may be debatable considering the absence of formal blinded controlled study. Here, we report the first randomized, double-blind, crossover study comparing DBS (stimulation "On") of the posterior hypothalamic region with a sham control (stimulation "Off"), followed by a 10-month open phase (stimulation "On") with a special focus on the procedure's safety.

Methods

Patients

Patients with refractory chronic CH were enrolled in the study according to the following inclusion criteria: chronic CH according to ICHD-II criteria [2]; disease duration over 3 years; resistance to pharmacological prophylactic treatment with adequate trials (verapamil up to 960 mg/day, lithium with plasma level from 0.6 to 1 mEq/l, association of both; in absence of adverse events); daily attacks; absence of substance abuse or dependence; age 18–65-year-old; normal findings on magnetic resonance imaging; no contraindications to surgery or anesthesia.

Study design

This study consisted of a randomized, double-blind, crossover design with two 1-month periods separated by a 1-week wash-out period and an extension 10-month open phase (Fig. 1). The trial was conducted in four academic centers in accordance with the Declaration of Helsinki, and was approved by the ethics committee of the Nice University Hospital (Comité de Protection des Personnes Sud Méditerranée V). All centers associated a neurological team belonging to the "Observatoire des Migraines et Céphalées" set up by the French Headache Society [15] and a neurosurgical team highly qualified in the DBS domain and pain management.

All patients provided written informed consent. Eligible patients were randomly assigned in a 1:1 ratio to one of the two groups; either active stimulation followed by a sham-stimulation period (On–Off) or the reverse other (Off–On). Previous studies [9, 11, 12] demonstrated that posterior hypothalamic stimulation does not induce perceptible sensations, allowing double-blind trial as the patient is not able to identify the "on" or "off" condition. We used a blocking scheme randomization and a central randomization procedure without stratification. Stimulation parameters were set up by the neurosurgeon. The 1-month duration of the randomized periods was defined according to the data available when the study was designed. At that time, in 2003, in the study of Franzini et al. [9], "pain disappearance … occurred after few hours in 2 cases and later (1–4 weeks) in the other 3 cases". In the study of Schoenen et al. [11], "all patients improved 2 weeks after implantation". Clinical evaluation was performed by the neurologist blinded of the stimulation status. At each evaluation, clinical data collected were: number of attacks during the last week (calculated from the individual patient's diary), mean attack intensity during the last week (according to Likert scale), number of subcutaneous sumatriptan administration during the last week (from the patient's diary), oxygen use (yes or no), anxiety and depression levels (Hospital Anxiety Depression scale), quality of life (SF-12 scale), supine and standing blood pressure, heart rate, weight and body temperature. Electrolyte balance and hormonal functions (thyroid hormones, TSH, ACTH, cortisol, SDHEA, insulin, prolactin, testosterone, estradiol,

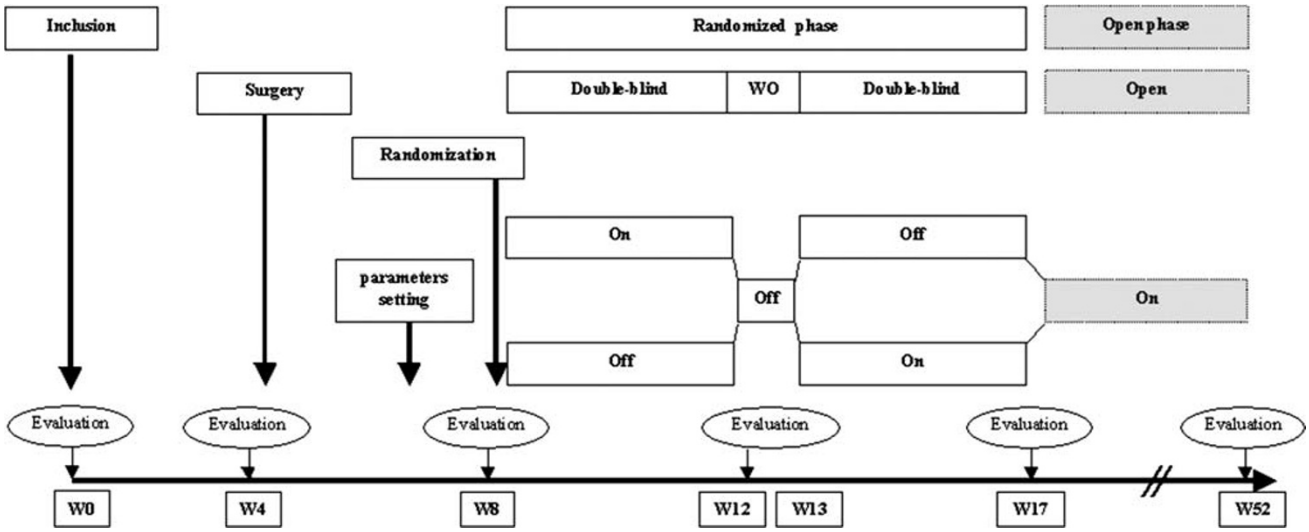

Fig. 1 Design of the study. The randomized phase of the study included two 1-month treatment periods (week 8 to week 12 and week 13 to week 17) separated by a 1-week washout period. Patients were evaluated at inclusion, 1 week before surgery; 4 weeks after surgery (before active or sham stimulation) and at the end of the first randomization period (weeks 12 and 17). This randomized phase was followed by a 10-month open phase. Patients were evaluated at the end of this phase (week 52)

LH, FSH, GH and IGF-1) were evaluated at each evaluation. After surgery, evaluations additionally included: patient's satisfaction (Patient's Global Impression of Change) and changes in thirst, appetite, libido, sleep-walking cycle and behavior. Any new symptom or worsening of a preexisting symptom was classified as an adverse event. An adverse event was classified as serious in case of death, hospitalization, sequel or consideration as serious by the clinician. According to the study protocol, prophylactic treatment was held constant during the randomized phase, but could be adapted during the open phase.

Surgery and stimulation

The posterior hypothalamus was targeted on preoperative 3D MRI, according to previously published coordinates, namely 2 mm lateral to the midline, 3 mm posterior and 5 mm below the mid-commissural point [9]. The four-contact electrode (model 3389 DBS, Medtronic) was implanted stereotactically (deepest contact on the target), ipsilateral to the pain side, under local anesthesia, without intraoperative micro-recording (Fig. 2). Intraoperative test stimulation (up to 3 V) was conducted through this electrode before its fixation to check any side effect. The electrode location was confirmed by postoperative 3D neuroimaging before its connection to the pulse generator (Kinetra, Medtronic), implanted under general anesthesia. Optimal stimulation parameters were defined by the neurosurgeon during the week following surgery before the randomization. The closest contact from the theoretical target on postoperative imaging was used for stimulation in the randomized phase. Stimulation frequency and pulse duration were, respectively, 185 Hz and 60 μs. Voltage was individually adjusted according to side effects investigated by increasing voltage: 3 V by default or 80% of the threshold producing side effects. These stimulation parameters were kept constant during all along the randomized phase, but could be changed during the open phase.

Outcome and statistical analysis

All outcome measures were analyzed by intention to treat. We performed a crossover analysis for the On and Off periods. Primary outcome was the number of attacks during the last week of each period, according to the International Headache Society guidelines for controlled trials of drugs in CH [16]. Secondary outcomes were the number of subcutaneous sumatriptan administration during the last week, intensity of attacks, satisfaction of patients, HAD sub-scores and SF-12 scores. Review of the early DBS studies [9, 11] in CH, available when the present study has been designed, did not allow to find the mean and variability of our primary outcome, namely frequency of attacks per week, in this refractory CH patients candidates for surgery. Due to absence of published data, this estimate was based on the characteristics of refractory chronic CH patients registered in the Nice University Hospital database. Power calculation was based on our estimate that at baseline mean weekly frequency of attacks would be 23.9 (SD 3.7). The study was designed to have an overall power of 90% to detect a 50% reduction of the primary endpoint during the stimulation period. According to Jones and Kenward [17], three effects were tested: carry-over, period

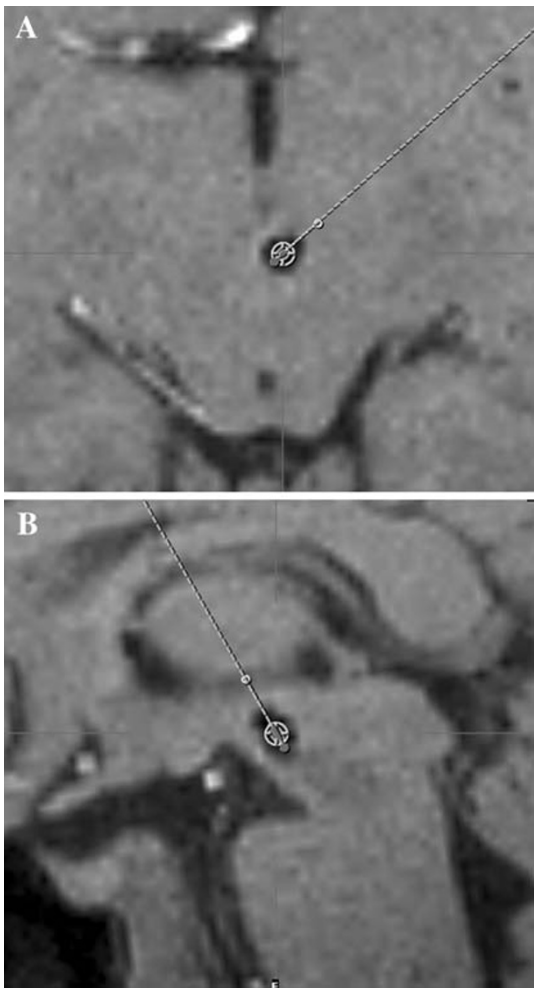

Fig. 2 Postoperative tridimensional MRI (patient C1P4), T1 weighted images after gadolinium injection, axial (**a**) and saggital (**b**) slices, showing the location of the stimulating contact (*white circle*) within the black artifact generated by the electrode. *Dotted line* indicates the projection of the electrode trajectory on the slice

and treatment effects. Type I error was fixed at 10% for the carry-over effect and 5% for the others. Non-parametric two-sided Wilcoxon rank-sum tests were used for the analysis, given the number of patients. The effect of treatment at 1 year compared to baseline was done with a Wilcoxon test for paired samples (two-sided, type I error rate = 5%) on primary and second outcomes. All the statistical analysis was performed using the SPSS version 11.0 program (SPSS Inc., Chicago, IL, USA).

Results

Study population

Twelve patients were included (May 2005–June 2007), 1 declined to participate, 11 were operated, 1 was explanted due to infection but re-implanted later, before the randomization. Consequently 11 patients completed the randomized phase and the open phase. Pre-implantation clinical characteristics of these 11 patients are shown in Table 1. According to the inclusion criteria, the patients included were non-responders to verapamil and lithium. However, considering the duration of chronic CH, all these patients have been previously treated in sufficient dosages (unless contraindicated or unacceptable side effects) alone or in combination by gabapentine, indometacine, methysergide, pizotifen, topiramate, steroids and valproate, and were considered as non-responders. There was no significant difference in these characteristics between the two groups (On–Off and Off–On).

Effect of electrode implantation

Mean stereotactic coordinates (SD) of the deeper contact of the electrode relative to the mid-commissural point were $x = 2.20$ (0.83), $y = -3.24$ (1.83) and $z = -3.69$ (1.71). There was no significant change in the mean weekly frequency of attacks after implantation compared to baseline, although two patients (C1P4 and C4P1) still showed a "lesion effect" (decrease $\geq$50%) 1 month after surgery.

Effect of the stimulation during the randomized phase

At the end of the randomized phase, patients and neurologists were not able to identify their period allocation, confirming the double-blind evaluation. The weekly frequency of CH attacks did not significantly differ between the On and Off periods (Table 2). We did not detect any significant carry-over effect ($P = 0.855$) indicating that the effects of the first treatment period did not persist after the wash out. None of the secondary outcomes differed between stimulation and sham treatment. Stimulation voltages used during the randomized phase ranged from 1.0 to 2.8.

Effect of the stimulation during the open phase

At the end of the 10-month open phase, the mean weekly attacks frequency decreased by 48.4% ($P = 0.08$) and emotional impact was significantly reduced (Table 3). Other secondary outcomes did not change significantly. Six out of 11 patients were considered as responders (at least 50% decrease in weekly attacks frequency), including three pain-free patients (Fig. 3). Among these 6 patients, prophylactic treatment was stopped or dose-decreased $\geq$50% in 2, unchanged in 2 and modified in 2 (Table 4). We did not identify any predictive factor of efficacy in this small population, concerning clinical characteristics, stimulation parameters or electrode location.

Table 1 Characteristics of the 11 patients before implantation

Center/ patient no.	Group	Sex	Age (years)	Disease duration (years)	Attack side	Onset clinical form	Attacks/ week	Pain intensity	Sumatriptan injection/ week	Oxygen use
C1/P1	On/Off	M	52	35	Left	Episodic	14	9	1	No
C1/P2	Off/On	M	40	12	Right	Chronic	14	5	14	No
C1/P3	Off/On	M	51	8	Left	Episodic	19	2	15	No
C1/P4	On/Off	M	44	10	Left	Chronic	28	10	0	No
C1/P5	On/Off	M	47	7	Right	Chronic	11	6	11	No
C2/P1	Off/On	M	50	20	Right	Episodic	20	5	0	No
C2/P2	Off/On	F	42	3	Left	Chronic	7	8	1	Yes
C3/P1	On/Off	F	42	7	Right	Episodic	53	6.5	0	Yes
C3/P2	Off/On	M	36	7	Left	Chronic	9	5	11	No
C4/P1	Off/On	M	39	18	Right	Episodic	14	5	14	No
C4/P2	On/Off	F	43	6	Right	Chronic	7	7	1	Yes
Mean			44.1	12.1			17.8	6.1	6.2	

Some patients did not use attack treatment by sumatriptan and/or oxygen due to their lack of efficacy or side effects (such patients used opioids with weak efficacy)

Adverse events

Three serious adverse events were reported during the study, in two patients. One subcutaneous infection, 3 weeks after surgery, completely resolved after hardware removal and antibiotic treatment. The patient was re-implanted 6 months later. One patient experienced a preoperative loss of consciousness with hemiparesia shortly after test stimulation. An immediate CT-scan was normal. Symptoms spontaneously resolved in 2 h without sequel. During the open phase, the same patient reported multiple severe micturition syncopes associated with decrease of blood pressure in standing position.

Twenty-six non-serious adverse events (NSAE) were reported (Table 5). All of them were mild, and most of them were transient. Rates of NSAE were similar in both "On" and "Off" randomized periods. Compared to baseline, no change in electrolyte balance and hormonal levels were detected, except a testosterone level increase, observed in one patient during the "off" period and open phase. According to behavioral systematic auto-evaluation, 7/11 patients reported a "calming effect" at the end of the open phase, compared to baseline.

Discussion

In the controlled phase of this study, we failed to demonstrate that DBS improved chronic CH when compared with sham stimulation. These findings contrasted with the results observed in the open phase of the study, which showed that more than 50% of the patients were improved over 50%, and that mean attack frequency and emotional impact were markedly decreased. Our long-term results were similar with the overall outcome of the 38 patients with chronic CH previously implanted in non-controlled conditions, showing that about 60% of them were improved over 50% [10, 14]. This improvement observed in the open phase was unlikely due to natural variations of the severity of chronic CH, because the attack frequency had been stable for more than 3 years before the inclusion in the study. Open phase improvement was unlikely due to prophylactic treatment changes because in four out of six responders, this treatment was stopped, dose-decreased or unchanged. However, the improvement observed at the end of the open phase could be related to a sustained placebo effect, sometimes described in headache trials [18]. Although one could speculate that DBS is ineffective in chronic CH, several bias, mainly related to the study design, might explain that efficacy of DBS has not been demonstrated in the randomized phase. First, the small sample size could have lead to inconclusive results in the randomized phase. Due to the lack of published data concerning this sub-population of refractory chronic CH patients, sample size calculation was based on the estimation of characteristics of these CH patients, registered in our institution database. Considering that the variability of weekly attack frequency was higher in the included population (SD: 13.2) than the estimated one (SD: 3.7), the sample size calculation might be a posteriori not adequate. Second, early publications, available when the study protocol has been written, mentioned that the delay between the stimulation onset and the therapeutic effect was less than 4 weeks, allowing to design a trial with 1-month periods [9, 11]. In later publications, this delay was longer (mean

Table 2 Changes in severity of cluster headache, emotional impact and quality of life during the randomized phase

	Active stimulation followed by sham stimulation (On–Off group) ($n = 5$) Median [range]			Sham stimulation followed by active stimulation (Off–On group) ($n = 6$) Median [range]			Difference between active and sham stimulation in the On–Off group Mean [95% CI]	Difference between active and sham stimulation in the Off–On group Mean [95% CI]	*P* value (treatment effect)
	Baseline (week 8)	End of On period (week 12)	End of Off period (week 17)	Baseline (week 8)	End of Off period (week 12)	End of On period (week 17)			
Attacks/week	11 [2–42]	18 [1–55]	6 [1–49]	16 [7–25]	14.5 [0–28]	9 [6–21]	0.2 [−24.0; 23.6]	−2.7 [−25.7; 20.31]	0.927
Sumatriptan (injection/week)	7 [1–13]	0 [0–18]	1 [0–6]	11.5 [1–29]	12.5 [0–33]	6.5 [0–25]	2 [−9.0; 13]	−5.3 [−24.1; 13.5]	0.349
Pain intensity	5.5 [4–9]	5 [3–8]	5.5 [3–8]	6 [2–9]	5.7 [0–10]	4.5 [2–9]	0 [−1.4; 1.4]	0.3 [−9.5; 10]	0.357
PGIC	na	2 [1–7]	2 [1–6]	na	2 [1–4]	4 [1–7]	0.8 [−20.1; 21.8]	1.3 [−4.2; 6.8]	0.853
HAD-A	8.8 [5–10]	8 [3–12]	6 [4–14]	11.5 [6–15]	8 [5–10]	9 [6–15]	0.2 [−23.6.1; 24.0]	−2.6 [−25.5; 20.3]	0.927
HAD-D	8.5 [3–13]	9 [4–13]	1 [0–6]	9.5 [1–13]	4 [1–9]	8 [1–16]	1.3 [−22.4; 25.1]	5.3 [−1.08; 11.7]	0.154
SF 12-MS	33.1 [28.1–52.1]	34.5 [31.6–56.2]	30.3 [17.8–59.9]	36.4 [27.5–53.3]	48.9 [24.9–54.2]	36.7 [16–52.9]	5.8 [−12.8; 24.4]	−8.7 [−27.3; 9.9]	0.197
SF 12-PS	29 [24.4–31.2]	28.3 [27.2–29.0]	33.8 [27.5–34.9]	34.7 [32.2–46.5]	37.9 [28.4–46.5]	43.4 [28.1–51.5]	−3.9 [−13.1; 5.3]	2.8 [−15.4; 21]	0.197

All carryover and period effects were not significant. *P* values are for the between-group comparison of the difference between active and sham stimulation during the last week of each period (weeks 12 and 17). Severity of chronic CH has been assessed by weekly attack frequency, pain intensity (Liekert scale), and weekly sumatriptan injections. Patient impression of change was recorded using the PGIC which is a 7-point scale (*1* extreme improvement; *2* significant improvement; *3* mild improvement; *4* no change; *5* mild worsening; *6* significant worsening; *7* extreme worsening). Emotional impact was assessed by the French version of the widely used Hospital Anxiety and Depression scale (HAD). The HAD involves seven anxiety items alternating with seven depression items. Anxiety and depression are defined by anxiety (HAD-A) and depression (HAD-D) scores superior to 7, respectively. The health-related quality of life was evaluated using the French version of the short-form 12 questionnaire (SF12) used to derive to summary scores, physical (SF12-PS) and mental (SF12-MS) component summaries. Lower numbers indicate greater disability

Table 3 Changes in severity of cluster headache, emotional impact and quality of life, between baseline (before surgery) and the end of the open phase

	Before implantation (week 4) Median [range]	End of open phase (week 52) Median [range]	Difference between end of open phase and baseline Mean [95% CI]	*P* value
Attacks/week	14 [7; 53]	8 [0; 23]	8.16 [–18.3; 34.7]	0.082
Pain intensity	6 [2; 10]	4.5 [0; 10]	1.1 [–7.1; 9.3]	0.499
Sumatriptan (injections/week)	1 [0; 15]	0.5 [0; 26]	–0.1 [–11.3; 11.1]	0.288
HAD-A	13 [5; 18]	7.5 [0; 14]	6.3 [–5.1; 17.7]	0.008
HAD-D	10 [1; 16]	4.5 [1; 15]	4.1 [–6.48; 14.7]	0.052
SF12-MS	33.2 [27.5; 53.3]	37.0 [20.7; 56.6]	–0.6 [–26.5; 25.2]	0.953
SF12-PS	32.7 [24.4; 46.5]	39.7 [25.2; 50.5]	4.3 [–16.7; 25.3]	0.173

Severity of chronic CH has been assessed by weekly attack frequency, pain intensity (Liekert scale), and weekly sumatriptan injections, during the last week before surgery and at the end of the open phase. Emotional impact was assessed by the French version of the widely used Hospital Anxiety and Depression scale (HAD). The HAD involves seven anxiety items alternating with seven depression items. Anxiety and depression are defined by anxiety (HAD-A) and depression (HAD-D) scores superior to 7, respectively. The health-related quality of life was evaluated using the French version of the short-form 12 questionnaire (SF12) used to derive to summary scores, physical (SF12-PS) and mental (SF12-MS) component summaries. Lower numbers indicate greater disability

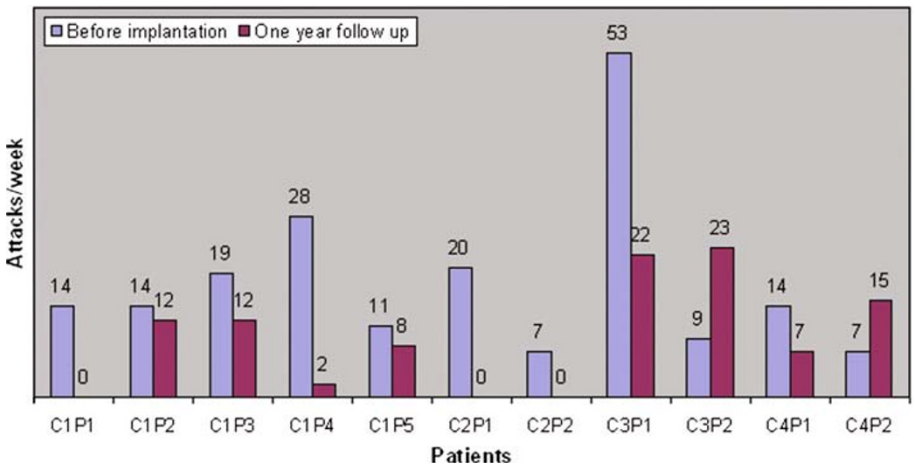

Fig. 3 Individual changes in weekly attack frequency in the 11 patients between baseline (before surgery) and the end of the open phase

42 days) [19]. Consequently, a 1-month period might be too short to observe a significant improvement. Finally, stimulation parameters used during the randomized phase were set by default, based on the ones previously reported [9, 11]. During the open phase, tedious individual "trial and error"-based adjustment of these parameters allowed to reach the expected efficacy. Consequently, the randomized phase might have been conducted using non-optimal parameters in some patients. Considering these possible biases, we proposed (after approval of the ethical committee) to the six responders in the open phase to be included in a new randomized phase, consisting in switching off the stimulator in control and double-blind conditions. All of them refused, fearing to loose the therapeutic effect.

DBS for CH appeared to be relatively safe in this study. No intracranial hemorrhage occurred, although this complication has been reported in early studies [11, 19]. In contrast to these studies, we did not use microelectrode recording in order to decrease the risk of bleeding, probably higher in this region. The most frequent adverse events (mainly visual disturbances) were stimulation-related and disappeared with stimulation parameters adjustment. Transient hemiparesia and loss of consciousness occurred during test stimulation in one patient, as in one case described by Starr et al. [12]. Micturition syncopes observed in one patient were probably related to changes in autonomic responses on cardiovascular system induced by chronic DBS [20]. No other clinically significant changes in homeostatic and hormonal functions were observed

Table 4 Changes in prophylactic treatment (drug and daily dose) between baseline and the end of the open phase

Patient	Long-term responder	Before implantation	1-year follow-up
C1P1	Yes	Verapamil 240 mg Lithium 800 mg	No treatment
C1P2	No	Verapamil 1440 mg	Verapamil 1440 mg
C1P3	No	Verapamil 1200 mg	Verapamil 1200 mg
C1P4	Yes	Verapamil 600 mg Lithium 400 mg	Verapamil 1080 mg
C1P5	No	Verapamil 720 mg Lithium 800 mg	No treatment
C2P1	Yes	Verapamil 960 mg Lithium 1000 mg	Verapamil 360 mg Lithium 500 mg
C2P2	Yes	Lithium 800 mg	Divalproex 1500 mg Fluoxetine 40 mg
C3P1	Yes	Verapamil 360 mg Prednisone 20 mg	Verapamil 360 mg
C3P2	No	Verapamil 480 mg	Verapamil 480 mg
C4P1	Yes	Verapamil 720 mg	Verapamil 720 mg
C4P2	No	No	Verapamil 240 mg

Long-term responders were defined as patients with weekly attack frequency decrease ≥50% at the end of the open phase, compared to baseline

despite an active surveillance of harms based on structured questionnaires and diagnostic tests performed at pre-specified time intervals all along the study.

CH has been described as the most painful primary headache, with a risk of suicide during attacks, justifying the moniker of "suicide headache" [21]. Considering our inclusion criteria and the patients' history (see "Study population"), all the patients included in our study fulfilled the criteria of intractable CH defined by international experts panels [22, 23], except for melatonin use (not available in France). In such patients, due to pain severity, absence of remission and treatment resistance, surgery may be a feasible option for pain control. Consequently, considering the safety and long-term outcomes of DBS in our study, the balance of benefit and harms may be considered as positive. This justifies to further evaluate DBS in additional controlled studies, using longer randomized periods or an initial open phase allowing enriched enrollment followed by a randomized phase. Predictors of outcome (headache characteristics, responses to medication and functional imaging features) need to be identified in order to select the potential responders [24]. However, future DBS studies should take into consideration the recent development of less invasive procedures, as occipital nerve subcutaneous stimulation (ONS) [25, 26]. Although the ONS efficacy remains to be confirmed in controlled conditions, DBS may be reserved for failure of ONS.

Table 5 Adverse events

AE related to surgery	2
Superficial infection (hardware removal) (SAE)	1
Neck pain along the lead	1
Transient AE related to test stimulation	5
(Resolving after voltage reduction or contact change)	
Complex oculomotor disturbances[a]	4
Loss of consciousness with hemiparesia (SAE)	1
AE and changes during "On" period	6
Mild hunger increase	3
Mild hunger decrease	1
Mild libido decrease	2
AE and changes during "Off" period	8
Mild hunger increase	2
Mild hunger decrease	1
Mild thirst increase	1
Mild thirst decrease	1
Mild libido decrease	1
Increased testosterone level	1
Shorten menstrual cycle	1
AE and changes related to chronic stimulation	8
Facial flush attacks	1
Changes in blood pressure response to posture	1
Severe micturition syncopes (SAE)	1
Basal blood pressure changes	0
Basal heart rate changes	0
Body temperature changes	0
Moderate weight increase (5 kg)	1
Mild hunger increase	1
Mild hunger decrease	1
Mild libido decrease	1
Significant electrolyte changes	0
Increased testosterone level	1
Other significant hormonal changes	0

SAE serious adverse event

[a] Three patients reported a transient diplopia, one reported an impairment of gaze fixation without objective oculomotor paresis

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