Cluster headache: expansion of the clinical spectrum

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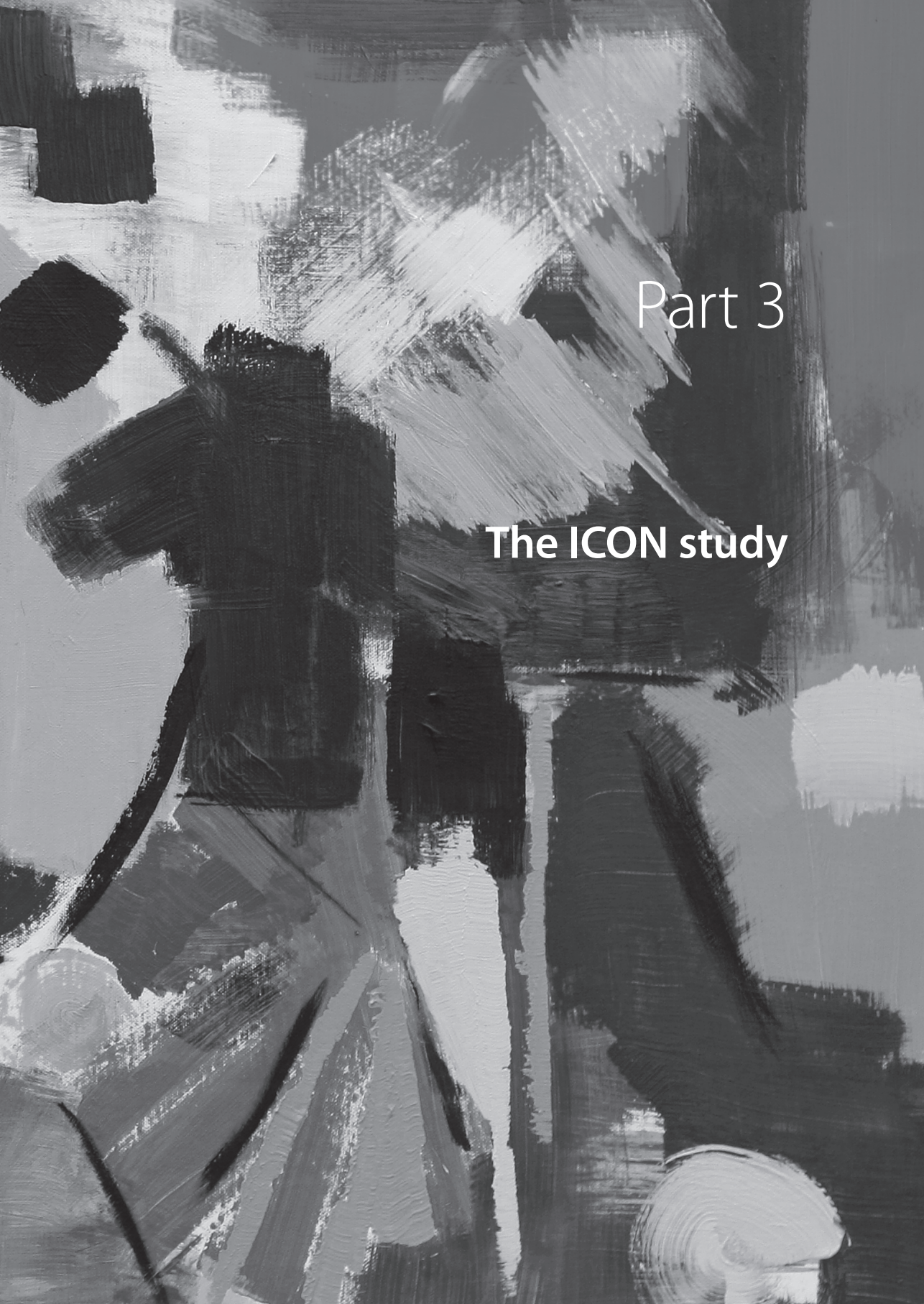

Part 3

The ICON study

Chapter 8

Occipital nerve stimulation in medically intractable, chronic cluster headache: The ICON study Rationale and protocol of a randomised trial

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Abstract

Background

About 10% of cluster headache patients have the chronic form. At least 10 % of this chronic group is intractable to or cannot tolerate medical treatment. Open pilot studies suggest that occipital nerve stimulation might offer effective prevention in these patients. Controlled neuromodulation studies in treatments inducing paraesthesias have a general problem in blinding. We have introduced a new design in pain neuromodulation in which we think we can overcome this problem.

Methods/ design

We propose a prospective, randomised, double blind, parallel group international clinical study in medically intractable, chronic cluster headache patients of high versus low amplitude occipital nerve stimulation. Primary outcome measure is the mean number of attacks over the last 4 weeks. After a study period of six months there is an open extension phase of 6 months. Alongside the randomized trial an economic evaluation study is performed.

Discussion

The ICON study will show if occipital nerve stimulation is an effective preventive therapy for patients suffering medically intractable chronic cluster headache and if there is a difference between high and low amplitude stimulation. The innovative design of the study will, for the first time, assess efficacy of occipital nerve stimulation in a blinded way.

Trial registration: Clinical trials.gov NCT01151631

Background

Cluster headache is a primary headache characterized by frequent short-lasting attacks of unilateral, severe headaches accompanied by ipsilateral cranial autonomic features of which the attacks mostly occur in bouts (episodic form).(1) Patients suffering the chronic form are no more than one month per year attack free without (effective) treatment.(2) Prevalence of cluster headache is about one in 500 and it is more prevalent in men.(3) Cluster headache has considerable socio-economic and personal impact.[4]

Effective acute treatments for cluster headache attacks are sumatriptan by injection(5) or nasal spray,(6) zolmitriptan by nasal spray(7) and oxygen inhalation. Verapamil, lithium carbonate, corticosteroids and methysergide (the last two only for a short period) are the most effective preventive therapies.(8) A subgroup of patients with chronic cluster headache is or may become intractable to or cannot tolerate medical therapy.(9) In these patients different experimental, invasive, non-pharmacological treatments that target the trigeminal nerve or the cranial parasympathetic outflow have been attempted. None of these procedures has been effective during long term observation and many have serious side effects.(10) Suboccipital injection of corticosteroid with local anaesthetics was shown to be effective in cluster headache patients, but unfortunately the attacks recurred after 3½ weeks in chronic cluster headache patients,(11) and such occipital nerve blockades are mainly regarded as bridging therapy between the regular prophylactic treatments.

Functional imaging studies in cluster headache have identified activations in the region of the posterior hypothalamus,(12) which has led to neurostimulation therapy in chronic cluster headache. Hypothalamic deep brain stimulation (DBS) was shown to be effective in some patients with medically intractable chronic cluster headache but unfortunately this treatment is associated with high (even lethal) risks.(13-15) That has led several groups to investigate less invasive and safer treatments, such as occipital nerve stimulation (ONS). A recent study indicated that ONS is probably even more effective than DBS in long term, with 80% of patients having 90% or more improvement in attack frequency in chronic cluster headache, but often there is a time delay of several months to get the optimal effect of ONS.(16) Several small, open studies

showed the same promising results of ONS in medically intractable chronic cluster headache and related headaches.(15, 17-19) No serious complications were described.

The rationale of ONS is based on human and animal studies which showed convergence of cervical, somatic trigeminal and dural trigeminovascular afferents on second order nociceptors in the brain stem.(20-22) Structures in the occipital region of the head are mainly innervated by the greater occipital nerve, a branch of the C2 spinal root. Stimulation of the greater occipital nerve increased metabolic activity in cervical regions of the spinal cord and in the trigeminal nucleus caudalis in the cat.(21) In humans an occipital nerve blockade decreased the ipsi- and contralateral R2 response of the blink reflex (a partly trigeminal dependant reflex), confirming the anatomic and functional convergence of afferent cervical and trigeminal pathways.(23) Magis et al.(24) performed a fluorodeoxyglucose positron emission tomography (PET) scan in ten medically intractable chronic cluster headache patients before and after ONS. This study showed normalisation of hypermetabolism in the midbrain, anterior cingulate cortex, left pulvinar, left visual cortex, cerebellum and ipsilateral pons after ONS, but not in the ipsilateral hypothalamus, which remained hyperactive. Switching off the stimulator had little influence on brain metabolism as compared to the on condition, which means there are no short term changes. This lack of short term changes supports the hypothesis that ONS acts through a slow neuromodulatory process in medically intractable chronic cluster headache.

A prospective, randomised, controlled trial (RCT) is necessary to assess the preventive efficacy, tolerability and safety of ONS in the treatment of well-defined medically intractable chronic cluster headache. As active ONS is associated with paraesthesias, it is difficult to conduct a blinded RCT. The present article describes the design and protocol of a double blind RCT of high and low intensity ONS in medically intractable chronic cluster headache patients. This study is the first blinded study of its kind. Alongside the randomized trial an economic evaluation study is performed. There are several advantages of publishing the design of an RCT before the results are available of which the most important are; it prevents publication bias and background and rationale of the study can be more extensively described. We introduce an innovative study design in pain neuromodulation.

Methods/design

The ICON study is a prospective, double-blind, parallel group multi-centre international RCT to compare the reduction in attack frequency from baseline of ONS in patients with medically intractable chronic cluster headache between two different stimulation conditions: high (100%) and low (30%) amplitude stimulation (Figure 1).

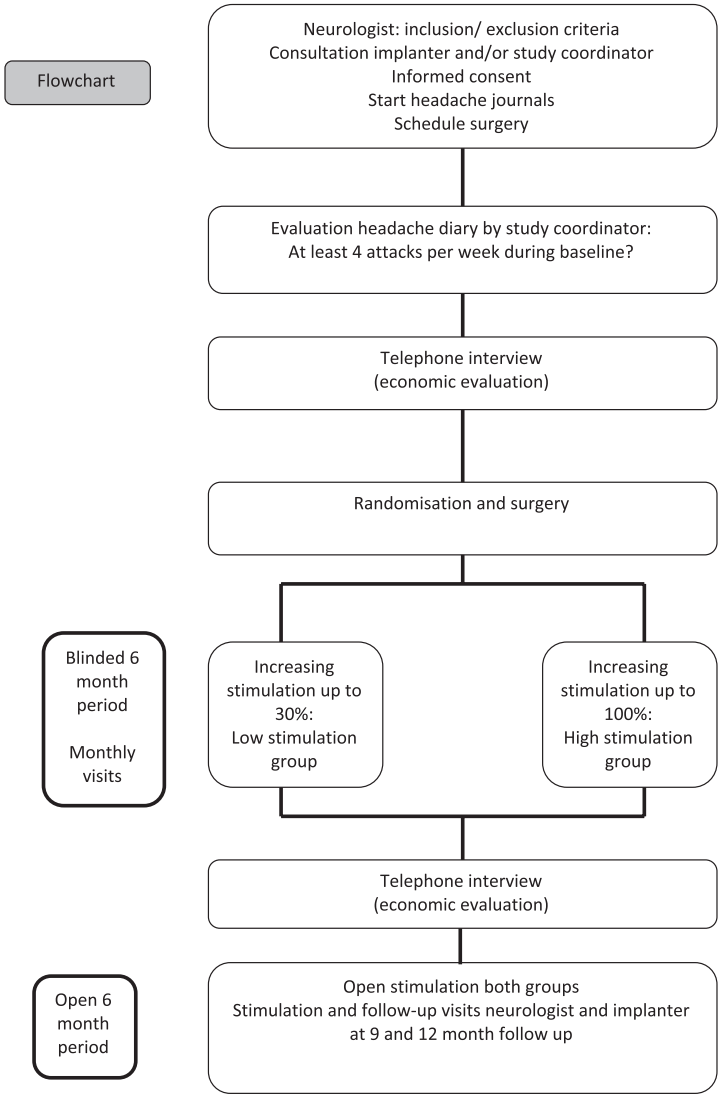

Figure 1. ICON study design

Rationale design

We have selected a 'high vs. low' stimulation design, instead of the more commonly used 'on vs. off' stimulation design, to minimise problems with unblinding due to the paraesthesias caused by neuromodulation. Patients are blinded to treatment allocation as they are unable to define the stimulation they receive to be high or low amplitude, because all are stimulation naive patients and all patients will experience paraesthesia in some extent. We hypothesize that there will be a difference in stimulation effect between high and low amplitude stimulation (dose-response relation). A previous similar 'high vs. low' stimulation design, albeit with a different technique and in a different patient group, was successfully used in a double-blind RCT which showed that high vagal nerve stimulation gave significantly more reduction in frequency of epileptic seizures than low vagal nerve stimulation.(25) Besides, Matharu et al.(26) showed a correlation between mean pain scores, stimulator induced paraesthesia and changes in regional cerebral blood flow. From these two studies we conclude that a dose related effect of neurostimulation exists and can justify the rationale of our design.

Patients and setting

Patients of 18 years or older suffering from medically intractable chronic cluster headache with at least 4 attacks per week and no abnormalities on brain MRI related to cluster headache, are eligible for this study (Table 1).(9) Patients will be recruited from tertiary headache clinics in the Netherlands and other European countries.

Ethical considerations

This study has been reviewed and approved by an independent ethical committee in accordance with the declaration of Helsinki. The design of this study has been approved by the Leiden Ethical Medical Committee and the local ethics committee from each participating centre. Informed consent is obtained from all patients before inclusion. There will be no financial rewards for the patients. Travel expenses will be compensated.

Table 1 Patient Selection Criteria

Inclusion Criteria
• ICHD-II criteria for chronic cluster headache • Mean attack frequency of 4 attacks per week or more • Minimum age18 years • Informed consent • Agreeing to refrain from starting new prophylactic cluster headache medication, including steroids, or any other therapy aimed at cluster headache and agreeing to maintain existing prophylactic cluster headache medication from 4 weeks before entering the baseline period throughout the duration of the double blind phase of the study. • Availability during follow-up period • An MRI not older than 4 years prior to enrolment must be available to exclude structural lesions potentially causing cluster headache. An exception can be made by the study coordinator in case of stable cluster headache for over 4 years and no change in symptoms after the last MRI scan was performed. • MRA of head and neck are to be performed according to study physician's individual judgement. • Medically intractable: Failed adequate trials of verapamil and lithium and one of the following: methysergide, topiramate or gabapentin.
Exclusion Criteria
• Other significant neurological or disabling diseases (including other forms of trigeminal autonomic cephalgias) which in the opinion of the clinician may interfere with the study • Pregnancy • Cardiac pacemaker and other neuromodulatory devices • Psychiatric or cognitive disorders and/or behavioural problems which in the opinion of the clinician may interfere with the study • Taking cluster headache prophylactic medication for conditions other than cluster headache which in the opinion of the clinician may interfere with the study • Serious drug habituation and/or overuse of acute headache medication (use on 10 or more days per month) for other headaches than cluster headache (excessive use of triptans for cluster headache attacks is not an exclusion criteria) • Inability to complete the (electronic) diary in an accurate manner • Structural intracranial or cervical vascular lesions that may potentially cause cluster headache • Previous destructive surgery involving the C2 or C3 roots (vertebrae) or deep brain stimulation • Enrolment in other clinical studies which in the opinion of the study clinician may confound the results of this study

Randomisation and blinding

Patients are randomly allocated to either high or low stimulation. Patients, neurologists and the study investigator are blinded for the results of randomisation. Randomisation will take place at the end of a baseline period and before implantation by obtaining the next available randomisation slot from the appropriate stratum in the pregenerated digital table. The programming of the stimulation (not blinded) is performed by the implanter (neurosurgeon or pain anaesthesiologist) or research nurse, and in order to keep the patients blinded, the programmers are instructed not to communicate with the patients regarding settings and/or outcome.

Patients are randomised using a variable blocked, balanced design stratified by hospital. Each stratum consists of fifty random blocks of four, six or eight patients. The randomisation table was generated and fixed by the study statistician before the first patient entered the trial.

Interventions

Participating surgeons will have a technical training and the first implantations are performed with the presence of an expert implanter (OT, GS).

Because of side shift of cluster headache attacks which sometimes occurs spontaneously and often after unilateral invasive treatments, bilateral implantation was chosen.(17) An abdominal or buttock location of the Implantable Pulse Generator (IPG) is proposed to and discussed with the patient. The procedure is performed under general anaesthesia and antibiotic prophylaxis and is done in two stages. First the patient is positioned with his/her head facing down. Using fluoroscopy the skin is marked at the level of vertebral body C1. Local anaesthetics are used before a small 3 cm cranio-caudal incision is made. A subcutaneous pocket is prepared. The Touhy needle is slightly bent and inserted in lateral direction just beneath the skin and outside the fascia. A Quad Plus® electrode (56 cm length, Medtronic) is inserted after the stylet is removed. The Touhy needle is removed with the lead in place and the lead is secured with a Titan anchor® which is fixed to the midline-fascia in the pocket with nonresorbable sutures. By slightly pulling the lead the fixation is checked. The same procedure is performed on the contralateral side. The lead is tunnelled subcutaneously to the left flank with the lead passer. The lead is looped at least two sites along the way, to avoid damage by possible traction. Finally all wounds are sutured. In a second stage the procedure is performed with the patient in a right lateral position (IPG placed in abdominal wall), or in supine position (IPG placed above the buttock). An incision is made at the marked site, a pocket is fashioned using blunt dissection in the subcutaneous fat layer over the abdominal fascia. The incision in the flank is re-opened and a small pocket is made there as well. From here the passer is inserted to the abdominal pocket. The lead extensions are pulled through and connected to the leads. The connection is covered by a silicon sheet fixed with nonresorbable sutures. The extension cables are connected to the IPG (Versitrel™ or Prime Advance™) which is implanted into the pocket and secured with nonresorbable

sutures. The N'vision™ programmer is used to measure impedances of the neuromodulation system. When the system is checked and found to have no failures, the remaining wounds are sutured.

Defining stimulation amplitudes

The amplitude of stimulation is established for each individual patient by determining the patient's individual acceptance range as previously described.[27] We verified reproducibility of this method in advance by defining perception and discomfort threshold repeatedly in ONS treated patients outside the ICON study. Stimulation frequency and pulse width are fixed at 60 hertz (Hz) and 450 microseconds (μs). The amplitude at which the patient starts feeling paraesthesias, is called the perception threshold. The amplitude at which the patient experiences uncomfortable stimulation is designated the discomfort threshold. Sub-pain-threshold is defined as 90% of the range between perception and discomfort thresholds. The stimulation range is chosen from perception threshold (0%) to sub-pain-threshold (100%), which will be established each visit to account for potential habituation of the stimulation. Consequently, 30% stimulation means a stimulation level at 30% of the range between perception threshold and sub-pain-threshold.

Stimulation Scheme

Following surgical implantation there will first be a run-in phase of 10 days of 10% stimulation intensity until wound check, followed by a stepwise increase up to either 30% (low stimulation arm) or 100% (high stimulation arm). Patients in the 100% stimulation arm will receive this intensity during 4 months.

Baseline data

Baseline data will assess demographics, weight and length, cluster headache characteristics, response to attack medication, duration of (chronic) cluster headache (years), smoking, alcohol and coffee use, familial cluster headache and concomitant types of headache.

Outcome assessment and economic evaluation

The patients will complete (electronic) diaries during the whole study period of 15 months: 3 months before implantation and 12 months follow-up. These questions consist of weekly headache diaries (frequency and intensity of

attacks) and four-weekly Short Form 36 (SF-36) to measure quality of life.(28) Additionally, during 3 periods of 6 weeks, (end of baseline, end of blinded part and end of study) each attack is documented by the patient: time and day, intensity and the use of attack medication. At six months follow up the patient will be asked about treatment allocations and at six and twelve months follow-up their opinion on recommending the treatment to a similar patient will be assessed on a 5 point scale. Patients will visit the pain clinic at 10 days, 1, 2, 4, 6, 9 and 12 months follow-up for stimulation adjustments and/or control of settings and, in addition, will have monthly follow ups during the blinded phase and at 3-monthly intervals during the open-label phase by the neurologist. There will also be an interview by telephone twice for economic evaluation at the end of baseline and blinded study period.

The primary outcome is the attack frequency during the last (6^{th}) month of the blinded period. Secondary outcome measures are the mean attack frequency for each 4 week period of the whole follow-up period, mean attack intensity, responder rate and other as mentioned in table 2.

Alongside the trial, an economic evaluation is performed from the societal perspective, which implies that all relevant costs and effects will be taken into account. The objective of the economic evaluation is to examine whether the delivery of high (100%) stimulation compared to low (30%) amplitude stimulation is preferable in terms of costs, effects and utilities from a societal perspective. This economic evaluation will involve a combination of a cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA). In a CEA effects are presented in clinical outcomes. The primary outcome measure for the cost-utility analysis will be Quality Adjusted Life Years (QALYs), based on the SF-36 utility scores.(28) Attached to this economic evaluation we will perform a cost-of-illness (COI) study, in which we will calculate the societal burden for medically intractable chronic cluster headache. For the economic evaluation as well as the cost-of-illness study we will use a retrospective cost questionnaire, which will include the PROductivity and DISease Questionnaire (PRODISQ) to measure production losses and other use of health care resources.(29)

Table 2 Secondary outcome measurements ICON study

Secondary outcome	*Description secondary outcome*
Mean attack frequency	The mean attack frequency for each 4 week period of the whole follow-up period.
Mean attack intensity	The mean attack intensity (on a scale from 0-10) will be calculated over the last 4 weeks for each group at baseline, 6 and 12 months follow up and will be compared between and within the 2 groups.
Responder rate	Rate of responders (>50% reduction in attack frequency in the last 4 weeks compared to baseline) will be calculated and compared between groups at 6 and 12 months.
Anticipated group randomisation	The patient and assessors will be asked at 6 months follow-up (before deblinding), in which treatment group (high or low stimulation) they think the patient was allocated.
Awareness of paraesthesias	Localisation and strength will also be evaluated weekly and coded through the patients' recordings in the electronic diary and compared with effectiveness of stimulation, e.g. frequency of attacks.
The use of acute attack medication	The number of doses of sumatriptan injections or intranasal spray or O_2 inhalation periods will be recorded of the last 4 weeks of each treatment period and the baseline period, for inter and intra group comparisons.
Patient satisfaction	At 6 and 12 months follow-up whether the patient would recommend the treatment to another patient using a 5 point (Likert) scale.
Responder identification	Whether predictive factors can be identified with respect to the outcome in a hypothesis generating manner. We will look at the body mass index (BMI) and assess the predictive value of response during the first weeks.
Adverse events	All and treatment-related adverse events will be documented by the investigators. Complications will be asked after every visit and recorded accurately. ONS most important, known, related risks include: lead migration, low battery, neck stiffness. Other possible complications are unpleasant sensations of paraesthesias, haematoma, limited neck movements, skin discomfort, hardware failure (e.g. early end of life of the battery, which can cause sudden increase of headache) and infection. A low battery has to be surgically replaced. This will eventually occur in all patients, so it can be debated if an empty battery must be considered as a complication.

Statistical analysis and sample size

Primary outcome. Baseline comparability will be assessed by descriptive statistics to determine whether randomisation indeed resulted in equal distributions of main variables. The aim of the study is [a] to prove that the treatment has a beneficial effect over follow-up time since start of treatment and [b] after [a] has been established, to prove that there is a dose-response effect (Figure 2). While [a] may be ascribed (at least in part) to a placebo effect, we believe that [b] cannot, since its associated effect measure is based on a between group comparison with random allocation to which the patient should be sufficiently blinded, therefore goal [b] is vital for the study to be successful. The analyses will take the general shape of a regression analysis with the mean attack frequency at six months as the dependent variable, the mean attack frequency at baseline as the covariate and treatment as a fixed factor.

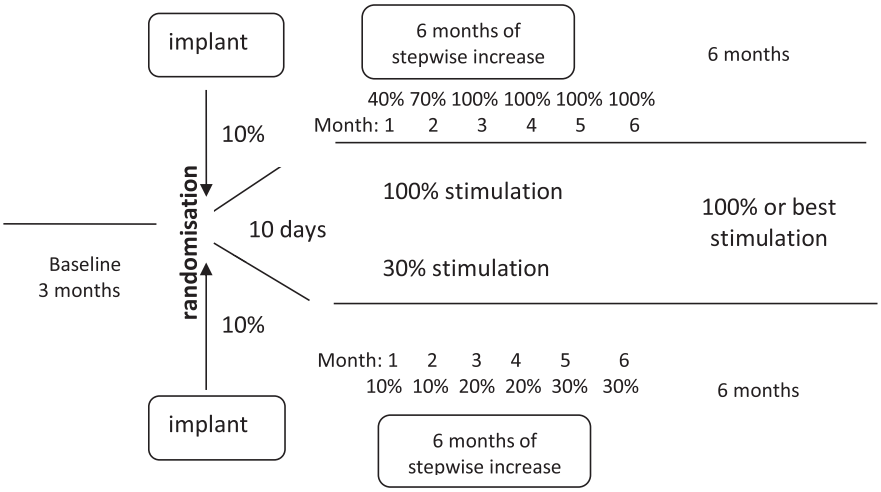

Figure 2. ICON study design

First we use an *F* test to evaluate (at the 5% level) the null-hypothesis [a] that there is no difference between the mean attack frequency at baseline and the mean attack frequency at six months follow-up. If this null-hypothesis is rejected, we test the following three null-hypotheses: [bI] there is no difference between the mean attack frequency at baseline and the mean attack frequency at six months follow-up in the low stimulation group, [bII] there is no difference between the mean attack frequency at baseline and the mean attack frequency at six months follow-up in the high stimulation group, [bIII] there is no difference between the mean attack frequency at six months follow-up between the low and high stimulation group. We will do this according to the closed testing principle.(30)

We will use an intention to treat approach in all our primary analyses. We will use a mixed model for repeated measurements, which takes missing values into account in a natural way. A per protocol analysis will be undertaken if substantial deviations from the allocated treatment or a substantial amount of missing values are observed to serve as a "sensitivity analysis".

Sample size. We conducted a small pilot study among all patients on the waiting list for this study at that time and found a mean weekly attack frequency of 26, with a standard deviation of 15, which was similar to a previous study.(18)

We performed our power calculation on the least powerful test of our primary analyses: the between group comparison [bIII] (see previous paragraph). We calculated that we will need 60 patients in each arm to detect a difference with probability of 90% if the standard deviation is 15 and the average of the difference in mean weekly attack frequency at six months between both groups (high vs. low amplitude stimulation) is 9 per week. Taking a possible 20% drop-out rate into account, we proposed a total study size of 144 subjects divided equally between both arms.

Secondary Outcomes. Apart from the primary analyses which focus on a specific time point (6 months), secondary analyses will take the full repeated measurements structure into account, including the 6 months values. We use a mixed model for repeated measurements with time since randomisation as a fixed covariate (or factor), MAF0 as a continuous covariate and Treat as a fixed factor.

All tests will be performed before unblinding.

Economic evaluation. To investigate whether data are normally distributed a Kolmogorov-Smirnov test will be performed. Despite the usual skewness in the distribution of costs, the arithmetic means will be generally considered the most appropriate measures to describe cost data.(31, 32) Therefore arithmetic means (and standard deviations) will be presented. In case of skewness of the cost data, non-parametric bootstrapping will be used to test for statistical differences in costs between the 100% stimulation and the 30% stimulation group.(33) The bootstrap replications will be used to calculate 95% confidence intervals around the costs (95% CI), based on the 2.5th and 97.5th percentiles. If cost data are distributed normally, t-tests will be used.

The incremental cost-effectiveness ratio (ICER) will be determined on the basis of incremental costs and effects of high stimulation compared to low stimulation. The ICER will be stated in terms of costs per outcome rate, the cost-utility ratio will focus on the net cost per QALY gained. The ICER will be calculated as follows. ICER = (Ci – Cc) / (Ei – Ec), where Ci is the annual total cost of the high stimulation group, Cc is the annual total cost of the low stimulation group, Ei is the effect at one year follow-up for the high stimulation group

and Ec is the effect at one year follow-up for the low stimulation group. The robustness of the ICER will be checked by non-parametric bootstrapping (1000 times). Bootstrap simulations will also be conducted in order to quantify the uncertainty around the ICER, yielding information about the joint distribution of cost and effect differences. The bootstrapped cost-effectiveness ratios will be subsequently plotted in a cost-effectiveness plane, in which the vertical line reflects the difference in costs and the horizontal line reflects the difference in effectiveness. The choice of treatment depends on the maximum amount of money that society is prepared to pay for a gain in effectiveness, which is called the ceiling ratio. Therefore, the bootstrapped ICERs will also be depicted in a cost-effectiveness acceptability curve showing the probability that high stimulation is cost-effective using a range of ceiling ratios.

Additionally, to demonstrate the robustness of our base-case findings a multi-way sensitivity analyses will be performed. In the sensitivity analysis uncertain factors of assumptions in the base case analysis will be recalculated in order to assess whether the assumptions have influenced the ICER, for example by varying cost-prices and volumes between minimum and maximum.(33)

Cost-of-illness (COI). The objective of this COI analysis is to calculate the societal costs of medically intractable chronic cluster headache. This prevalence based, retrospectively and bottom-up cost of illness study will be performed at baseline. Data for this COI will come from the baseline measurements of a cost questionnaire especially designed for this group, based on existing questionnaires, which will identify all relevant costs aspects.[29, 34] The valuation of the COI will be based on the same methods as used in the economic evaluation.(35)

Discussion

In this article the rationale and design of an ongoing double blind RCT on the preventive effect of ONS in medically intractable chronic cluster headache are described. The objective of this trial is to provide evidence for (cost-) effectiveness of ONS in medically intractable chronic cluster headache. It is important for this small, but severely suffering group of patients for whom

there is at present no established therapy, to offer them an effective treatment in the future. Until now, the only available data of possible efficacy of ONS come from small open studies, which are insufficient to prove effectiveness and classify ONS as a regular therapy. Nevertheless, ONS is already applied as a therapy for cluster headache patients worldwide, so we consider prove of its (lack of) efficacy also as an ethical matter. As blinding in neuromodulation studies of this kind is difficult because stimulation is felt by the patient as paraesthesia on the back of their head, it is not possible to perform a blinded study in which active stimulation is compared to no (sham) stimulation. We propose a way to perform a blinded study in neuromodulation by comparing high and low amplitude stimulation and establish a dose response curve in a blinded way. This design has been successfully used before in a vagal nerve stimulation study in epilepsy.(25) Unfortunately, that study did not include an evaluation whether the patient had recognized the allocated group, so it is unknown if blinding was successful. This 'high vs. low' stimulation design has some disadvantages. First, it is less powerful, so more patients are needed to detect a clinically relevant, significant difference. Second, we do not know for sure that high ONS is more effective than low ONS, as this is only based on a dose-response theory and never investigated before in cluster headache. An important advantage of this design, however, is that for the first time, it allows to assess efficacy of ONS in patients suffering from chronic cluster headache in a blinded way by eliminating a possible placebo effect. We also think that this design is preferable over study designs used in RCTs in ONS in migraine patients, in which active stimulation was compared to stimulation off after trial stimulation.(36) In the ONSTIM study patients were randomised to adjustable stimulation, preset stimulation (1 minute per day stimulation) and medical management.(37) In both studies the successfulness of blinding was not assessed. Patients in the placebo arm could have been unblinded by lack of paraesthesia. The ICON study may also answer the question whether high intensity occipital nerve stimulation is more (cost-) effective than low intensity occipital nerve stimulation.

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Author's contributions

LAW is the coordinator of the study and is responsible for collecting and analysing the data and for drafting the manuscript. MDF is the principal investigator. OPMT, JH, EWZ, SMAAE, GHS, PHV, WM, RB, FJPMH, RHJ, KP, PJG, VV, MDF designed and supervised the study. All authors read and approved the manuscript. RB is a non-voting observing member of the Steering Committee.

Conflict of Interest Statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: LAW received industry support from Medtronic, Menarini, Allergan and independent support from Fonds Nuts Ohra. JH received consultancy support from Merck. OPMT received support from Medtronic. SMAAE received several grants from ZonMw. GHS received support and consultancy from Medtronic. PHV received a grant form Medtronic. WM received support from Medtronic and MSD and consultancy from Merck. FJPMH received consultancy from spinal modulation, Grunenthal and MSD, grant from ANS St Jude, Royalties from evidence based medicine in invasive pain treatment, support from Pfizer and MSD. RHJ received support from EHMTIC 2012, FP-7 grant. KP received consultancy from Autonomic Technologies Inc. PJG has consulted for or lectured in sessions supported by Allergan, Colucid, MAP Pharma, Merck, Sharpe & Dohme, eNeura, Autonomic technologies, Boston Scientific, Eli-Lilly, Linde gases, BristolMyersSquib, Arteaus, AlderBio, Medtronic, Pfizer, Zogenix, Nevrocorp, Lundbeck, Impax, DrReddy, MSD, Mennarini and had grant support from GlaxoSmithKline, MAP Pharma, MSD, eNeura, Allergan and Amgen. MDF has, in the past 3 years, received grants and consultancy/industry support from Almirall, Coherex, Colucid, Eisai, GlaxoSmithKline, Linde, MAP, Medtronic, Menarini, Merck, Minster, Pfizer, and St Jude, and independent support from the Netherlands Organisation for Scientific Research (NWO). EWZ, RB, VV report no conflicts of interest.

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