Occipital nerve stimulation in medically intractable, chronic cluster headache

Published: 03-06-2010
Last updated: 02-05-2024

Primary: To demonstrate that high (100%) stimulation of ONS therapy reduces the mean attack frequency (MAF) in MICCH by at least 35% compared to low (30%) stimulation of ONS.Secondary: To evaluate • the rate of responders (>= 50% reduction in MAF…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Headaches
Study type	Interventional

Summary

ID

NL-OMON46990

Source
ToetsingOnline

Brief title
ICON

Condition

- Headaches

Synonym
cluster headache

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Medtronic,Medtronic B.V.

Intervention

Keyword: chronic cluster headache, occipital nerve stimulation

Outcome measures

Primary outcome

The primary endpoint is the mean attack frequency (MAF) over the last 4 weeks in the 100% and the 30% treatment groups.

Secondary outcome

MAF: We will repeat the primary analysis, with the MAF as outcome instead of the logarithm of the MAF.

MAF during follow-up: The MAF for each 4 week 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.

Economic evaluation

Anticipated group randomisation: The patient and assessors will be asked at 6 months follow-up (after 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 O2 will be investigated and calculated of the last 4 weeks of each treatment period and the baseline period, and compared between and within groups.

Patient satisfaction: We will ask the patient at 6 and 12 months follow-up whether he/she would recommend the treatment to another patient using a 4 point scale: strongly, moderately, mildly or not recommended.

Responder identification: It is also investigated whether predictive factors can be identified with respect to the outcome in a hypothesis generating manner.

Adverse events: All and treatment-related adverse events will be documented by the investigators.

Study description

Background summary

Cluster headache (CH) is a primary headache disorder characterized by recurrent short-lasting attacks (15 to 180 minutes) of excruciating unilateral periorbital pain accompanied by ipsilateral autonomic signs. The 1-year prevalence of CH is about 0.1 %, the male: female ratio is 3:1. The majority of patients have cluster periods of weeks to months with frequent attacks which are alternated with symptom-free periods of months to several years; the episodic from of CH. In about 10% of patients the CH is chronic (CCH) in which either no remission occurs within 1 year or the remissions last less than 1 month. At least 10 % of CCH patients are refractory to medical treatment or cannot tolerate the treatments.

Recent pilot studies suggest that occipital nerve stimulation (ONS) in medically intractable CCH (MICCH) might offer an effective alternative to medical treatment. There are no randomised clinical trials, a placebo effect cannot be excluded, and little is known about long term tolerability.

Here we propose a prospective, randomised, double blind, parallel group multi-centre international clinical study to compare the reduction in attack frequency from baseline of occipital nerve stimulation (ONS) in patients with MICCH between two different stimulation conditions: high (100%) and low (30%) stimulation.

We want to demonstrate that high (100%) stimulation of ONS therapy reduces the mean attack frequency (MAF) in MICCH by at least 35% compared to low (30%) stimulation of ONS.

Study objective

Primary:
To demonstrate that high (100%) stimulation of ONS therapy reduces the mean attack frequency (MAF) in MICCH by at least 35% compared to low (30%) stimulation of ONS.

Secondary:

To evaluate
• the rate of responders (>= 50% reduction in MAF)
• patient*s satisfaction
• mean pain intensity
• headache index (frequency of attacks times the pain intensity)
• medication use
• quality of life
• tolerability and safety of ONS therapy
• whether the patient would recommend the treatment to another patient
• predictive factors for efficacy
• cost-effectiveness, cost-utility and cost of illness

Study design

This is a prospective, randomised, double blind, parallel group multi-centre international clinical study to compare the reduction in attack frequency from baseline of occipital nerve stimulation (ONS) in patients with MICCH between two different stimulation conditions: high (100%) and low (30%) stimulation. Active ONS is associated with paraesthesias complicating blinded comparison versus no stimulation. We have reasons to believe that patients might find it difficult to differentiate paraesthesias associated with 100% and 30% stimulation. Recognition of the stimulation intensity would be further complicated by stepwise increasing the stimulation intensity.

Following implantation there will first be a run-in phase of 10 days of 10% stimulation intensity, followed by a stepwise monthly increase up to either 30% or 100%. Patients in the 100% stimulation arm will receive this intensity for 4 months. Patients will be assessed at 1, 2, 4 and 6 months by a blinded assessor. The primary outcome measure is the number of attacks over the last 4 weeks of the double blind 6 month treatment period. Hereafter, in an open extension phase of 6 months, all patients will receive 100% stimulation or the stimulation considered optimal by the patient.

Intervention

Surgery
All patients will undergo occipital Nerve Field Stimulation implant procedure. The eligible patient will have the procedure under general anaesthesia and antibiotic prophylaxis (Cephalozin 1 or 2 g according to local guidelines) will be given half an hour prior to the actual surgery. The surgery will be done in two tempi. First the patient is positioned front side down with his/her head facing downwards in an adjustable U shaped headrest. A small area is infiltrated with a mixture of lidocain(10mg/ml) /epinephrine(5mcg/ml) in the midline of the upper neck, before a small (2 cm) in a cranio-caudal incision is made. A 2-3 cm subcutaneous pocket is prepared. The Touhy needle is slightly bent and then using fluoroscopy inserted in lateral direction just beneath the skin and outside the fascia. The Quad Plus® (56 cm length) is inserted after the stylet is removed. It is advanced until all electrodes are covered, the Touhy needle is removed. The lead is secured with a Titan anchor® that is fixated to the midline fascia in the pocket with nonresorbable sutures (Mersilene® 1-0). By slightly pulling the lead the fixation is checked.

On the contralateral side, exactly the same procedure is performed. With the tunneler the lead is then subcutaneously led to the left flank, an in-between incision may be required. The lead is looped at all sites of the incision, to avoid damage though traction later on. Finally all wounds are sutured.

In a second tempus the patient is positioned laterally, right side facing down.

A 7-8 cm sideways incision is made at the marked site of the abdomen, a pocket (5x5 cm) is made using blunt dissection (no monopolar cautery allowed) in the subcutaneous fat layer over the abdominal fascia. The incision in the flank is re-opened and a small pocket (3x3 cm) is made here as well. From here the tunneler is inserted to the abdominal pocket. The lead extension is pulled through and connected to the lead. The connection is covered by a silicon sheet fixed with nonresorbable sutures. The extension cable is connected to the IPG (Versitrel*) which is implanted into the pocket and secured with 1 or 2 nonresorbable sutures. The N*vision* programmer is used to analyse impedances of this neuromodulation system. When there are no system failures, remaining wounds are sutured.

Study burden and risks

When it is decided that the patient can be included for the study, there will be an informed consent first. It will approximately take two months to schedule the surgery. The patient will undergo the pre-operative screening and will fill in a daily electronic diary for four weeks to practice first, followed by eight weeks before surgery. Randomisation will take place if the patients still fulfils eligibility criteria after filling in the pre-operative headache diary for 12 weeks. The surgery will be planned in advance because of potential waiting lists.

Pre-operative evaluation

• Written informed consent
• Common internal and neurological examination
• Pre-operative consultation of an anaesthesiologist
• MRI must be available (not older than 4 years) or performed and must be repeated after any changes in symptoms to exclude an underlying cause of the CCH. MRA of head and neck may be performed according to study physician*s individual judgement.
Questionnaire (in ProMISe):
• medical history, medication use now and in the past, course of the disease (Primairy CCH or Secondary CCH), social habits: smoking, alcohol, coffee, previous response to medication: intolerability or no or little response)
Electronic headache diary for 12 weeks (of which 4 are to practice) (in ProMISe):
• Each attack of CH
• Pain intensity (1-10) during the last 4 weeks
• Number of attacks per day of CH and other forms of headache
• Use of prophylactic or acute medication
• Monthly SF-36 questionnaire

Interview by telephone:
• A questionnaire about health consumption and absenteeism from work

Schedule
Visit 1: screening neurologist: inclusion/exclusion criteria

Visit 2: visit neurosurgeon (or implanter)/investigator: information about the surgery and study: reflection period of 7-14 days (or as long the patients needs)

Visit 3: informed consent. Start electronic diary

Visit 4: anaesthesiologist:

Evaluation headache diary by study coordinator: does the patient still meet inclusion criteria: at least 4 attacks per week?

Interview by telephone (medical student): economic evaluation questionnaire

Randomisation

Visit 5: surgery and defining stimulation parameters: 2-3 days in hospital

Visit 6: +10 days control of wound and removal of stitches t=0 and calibration of stimulation

Visit 7: + 1 month: checking and changing of stimulation follow-up

Visit 8: + 2 months checking and changing of stimulation follow-up

Visit 9: + 4 months: checking of stimulation follow-up

Interview by telephone (student) after 6 months: economic evaluation questionnaire

Visit 10: + 6 months: checking of stimulation follow-up

Open trial:

Visit 11: + 9 months: checking of stimulation follow-up

Visit 12: + 12 months: checking of stimulation follow-up

The patient will visit the study neurologist on a monthly basis during the first blinded period of the study

Interview by telephone
The patient will be interviewed by telephone twice by a medical student to answer a questionnaire about health consumption and absenteeism.

ONS most important, known, related risks include: lead migration, low battery, neck stiffness. The risk of lead migration is probably related to the surgery technique used. In a recent Dutch study in 4 patients treated with ONS, there was no lead migration (unpublished data) or any other complications after 1.5 year follow-up. 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. Other possible complications are unpleasant sensations of paraesthesias, haematoma, limited neck movements, skin discomfort and infection.

Treatment-as-usual related risks are related to the medication used and do not increase due to participation in this study.

Until now, no persistent iatrogenic neurological deficit has been reported using ONS.

Contacts

Public
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333 ZA
NL
Scientific
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333 ZA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• ICHD-II criteria for Chronic Cluster Headache
• Minimum mean attack frequency of 4 attacks per week
• Minimum age of 18 years old
• Signed study specific informed consent form agreeing to implantation of the device, data collection and follow-up requirements
• Agreeing to refrain from starting new prophylactic CH medication, including steroids, or any other therapy aimed at CH (such as acupuncture, biofeedback, chiropractic, or massage) and agrees to maintain existing prophylactic CH medication from 4 weeks before entering the baseline period throughout the duration of the double blind phase of the study. It is allowed to change the dose of prophylactic medication during the study based on the opinion of the treating medical specialist.
• Availability during follow-up period
• An MRI not older than 4 years prior to enrolment must be available to exclude structural lesions potentially causing CCH. MRA of head and neck are to be performed according to study physician*s individual judgement.
• Medically intractable (see below)
Adequate trial:
Appropriate dose and duration of treatment according to local guidelines, appropriate length of time, consideration of medication overuse;Failed:
No therapeutic or unsatisfactory effect, intolerable side effects, contraindications to use;Must have tried agents of at least three classes of the following, of which 1 and 2 are obligatory, and 1 should come from 3-5: (recommendation of Goadsby et al. applied to Dutch national guidelines);1 Verapamil
2 Lithium
3 Methysergide
4 Topiramate
5 Gabapentin

Exclusion criteria

• Other significant neurological or disabling diseases (including other forms of TAC) which in the opinion of the clinician may interfere with the study
• Pregnancy or the wish to become pregnant during the study period
• 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 CH prophylactic medication for conditions other than CH 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 CH

• Inability to complete the (electronic) diary in a sensible and accurate manner
• Structural intracranial or cervical vascular lesions that may potentially cause CH
• Previous destructive surgery involving the C2 or C3 roots (vertebrae) or trigeminal nerves
• Enrolment in other clinical studies (of an investigational drug or device, new indication for an approved drug or device, or requirement of additional testing beyond standard clinical practice) during the study or within four weeks prior to his/her enrolment in the study
• Requiring anticoagulation therapy or antithrombotic or thrombocyte aggregation-inhibitor for a concomitant condition that cannot be stopped peri-operatively. The local peri-operative protocol of each individual participating centre will be followed

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-10-2010
Enrollment:	120
Type:	Actual

Medical products/devices used

Generic name:	unilateral quad plus connected to versitrel/ prime advanced IPG
Registration:	Yes - CE outside intended use

Ethics review

Approved WMO Date:	03-06-2010
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	29-02-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	11-07-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	18-03-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	20-03-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	31-10-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

	metc-ldd@lumc.nl
Approved WMO Date:	11-02-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	06-04-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	21-06-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT01151631

Register
CCMO

ID
NL30794.058.10