Chronification and reversibility of migraine.

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON22952

Source
NTR

Brief title
CHARM

Health condition

(chronic) migraine, migraine, medication-overuse headache

Sponsors and support

Primary sponsor: Leiden university Medical Center
Source(s) of monetary or material Support: NWO VIDI grant

Intervention

Outcome measures

Primary outcome

The primary outcome measure is the relative reduction in headache days per month, in a comparison of the last month of withdrawal (month 3) with the baseline period (month -1). A headache day is defined as a day on which there is at least one period of ≥ 4 hours of continuous headache. The relative reduction will be measured in the Btx and placebo groups and will be adjusted using multivariate analysis for depression scores at baseline and support

by the headache nurse. As an alternative primary outcome measure, we will measure quality of life during the withdrawal trial. This will be measured by the Sumscore on the SF-36 questionnaire at timepoint 0, 1, 2 and 3.

Addendum: The primary outcome measure is the relative reduction in headache days per month, in a comparison of the last month of withdrawal (month 3) with the baseline period (month -1). A headache day is defined as a day on which there is migraine or non-migraine headache . The relative reduction will be measured in the Btx and placebo groups and will be adjusted using multivariate analysis for depression, anxiety, gender, age, headache days at baseline and support by the headache nurse.

Secondary outcome

The differences between Btx and placebo groups will be assessed by measuring absolute and relative reduction in migraine and headache days on time points 3, 6, 9 and 12, the number of patients achieving a 50% or more decrease from baseline (month -1) in the frequency of migraine days and migraine episodes at time points 3 and 12 and absolute and relative reductions of HIT-6, CES-D and HADS-D scores at time points 3, 6, 9 and 12 and changes in these scores during the withdrawal trial. Also subjective satisfaction with both treatment and treatment outcome will be assessed.

The difference between maximal versus minimal support by a headache nurse, responders (≥50% reduction in headache days) versus non-responders and depressive (HADS≥8) versus non-depressive chronic migraineurs will be assessed by measuring the absolute and relative reduction in migraine and headache days on time points 3, 6, 9 and 12, the number of patients achieving a 50% or more decrease from baseline (month -1) in the frequency of migraine days and migraine episodes at both time points and absolute and relative reductions of HIT-6, SF-36 CES-D and HADS-D scores at time points 3, 6, 9 and 12.

Headache relapse rates at t=12 will be assessed and compared between Btx and placebo-treatment, minimal or maximal support by the headache nurse and depressive versus non-depressive groups.

The change in reactiveness of the trigeminal blink reflex during the course of the trial will be assessed. Blink reflex will be tested at time points 0, 3 and 12.

Addendum: As a secondary outcome measure, we will measure quality of life during the withdrawal trial. This will be measured by the Sum scores on the SF-36 questionnaire at time point 3 compared to time point 0. The SF 36 questionnaire will be assessed at time points 6, 9 and 12 as well. Furthermore, he differences between Btx and placebo groups will be assessed by measuring absolute and relative reduction in migraine and headache days and the total duration of migraine and headache on time points 3, 6, 9 and 12, the number of patients achieving a 50% or more decrease from baseline (month -1) in the frequency of

migraine days and migraine episodes at time points 3 and 12 and absolute and relative reductions of HIT-6, CES-D and HADS-D scores at time points 3, 6, 9 and 12 and changes in these scores during the withdrawal trial. Also subjective satisfaction with both treatment and treatment outcome will be assessed.

Study description

Background summary

In this study we will perform a randomized, double blind, placebo-controlled trial in which chronic migraine patients (n=180) with medication overuse (OAHM) will be randomized to withdrawal therapy with accessory Botulinum toxin A (Btx) injections or with placebo-treatment, and minimal or maximal support of a headache nurse.

We will perform an MRI-study in the first 100 chronic migraineurs included, before and after withdrawal of medication. MRI will also be performed in matched control groups, consisting of patients with episodic migraine, patients with chronic pain, patients with a depressive disorder and healthy controls (n=20 for each control group) to correct for any bias by migraine specific, chronic pain related- or affective changes. Magnetic resonance imaging will be performed at baseline in all chronic migraineurs and control groups. The imaging protocol will be repeated in chronic migraineurs after completion of the withdrawal phase (at three months) and at one year after start of withdrawal to study short- and long term changes in that specific group. Blink reflexes (as a marker of excitability of the trigeminovascular system) will be tested at baseline in both the chronic migraine patients, and at 3 and 12 months in the chronic migraine patients. At the same time points as the blink reflex (ETVS) and MRI-scans, questionnaires will be taken and blood samples will be drawn.

Study objective

We want to unravel the role of depression and OAHM in the chronification of migraine, assess the (permanent and reversible) short- and long-term consequences of chronic migraine and OAHM on the brain, and decipher some of the underlying neurobiological mechanisms.

We hypothesize for the withdrawal phase, that:

1. Treatment with Botulinum toxin A (Btx) injections (at the start of the therapy) will increase the success rate of withdrawal therapy or will improve quality of life during the withdrawal period:

A. The presence of comorbid depressive symptoms is associated with a reduced success rate of withdrawal of OAHM in patients with chronic migraine;

B. The support of a headache nurse during the withdrawal period will increase the success rate of withdrawal therapy;

C. Presence of comorbid depressive symptoms, baseline migraine characteristics (e.g. attack frequency, duration of attacks, number of medication days per month) and baseline brain structure and function (BSF) and excitability of the trigeminovascular system (ETVS) measures are predictors of the success rate of withdrawal therapy.

We hypothesize for the baseline imaging phase, that:

2. Before treatment, changes in (regional) BSF and ETVS can be identified in chronic migraineurs with medication overuse. The use of different control groups (episodic migraineurs, depressive patients, chronic pain patients and healthy controls) will allow to differentiate changes in (specific) structures or functions associated with chronification of migraine from changes associated with depression and/or chronic pain.

We hypothesize for the longitudinal imaging phase, that:

3. After withdrawal, changes in BSF and ETVS compared to baseline will point towards transmutable structures or functions involved in and/or predisposing to chronification of migraine:

A. Changes in BSFB and ETVS after withdrawal therapy will depend on a) accompaniment of Btx injections and;

B. The presence of depressive symptoms;

C. Specific MRI markers of BSF correlate with measures of ETVS.

Study design

-1 month, 0, months 3, 6, 9, 12.

Addendum: The difference between maximal versus minimal support by a headache nurse, and depressive (HADS≥8) versus non-depressive chronic migraineurs will be assessed by measuring the absolute and relative reduction in migraine and headache days on time points 3, 6, 9 and 12, the number of patients achieving a 50% or more decrease from baseline (month -1) in the frequency of migraine days and migraine episodes at both time points and absolute and relative reductions of HIT-6, SF-36 CES-D and HADS-D scores at time points 3, 6, 9 and 12. The differences in baseline characteristics (i.e. headache characteristics, accompanying symptoms, depression, anxiety) between responders (≥50% reduction in headache days) versus non-responders will be examined.

Headache and medication overuse relapse rates at t=12 will be assessed and compared between Btx and placebo-treatment, minimal or maximal support by the headache nurse and depressive versus non-depressive groups. The change in reactiveness of the trigeminal blink reflex during the course of the trial will be assessed. Blink reflex will be tested at time points

0, 3 and 12.

Intervention

Participants will be randomized to receive either:

1. "Verum": Withdrawal therapy with one-time concommitant botulinum toxin A injections in 31 locations according to the injection protocol by Allergan (total 155U);

2. "Placebo": Withdrawal therapy with one-time concommitant low-dose botulinum toxin A injections in the facial region and NaCl injections in the other regions according to the injection protocol by Allergan (Total 17.5U).

Withdrawal therapy is considered standard treatment for this patientgroup and takes three months. During this time, patients will be guided by a trained headache-nurse.

At the end of the three-month withdrawal period, primary outcomes will be assessed. All participants who have succesfully completed the withdrawal period, but are still suffering from chronic migraines will be offered single treatment (open-label) with botulinum toxin A. This group will consist of participants from both the verum and placebo groups, but due to blinding, initial treatment is not known at this point).

Contacts

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Eligibility criteria

Inclusion criteria

Suffering from chronic migraine according to the ICHD-II criteria for chronic migraine with medication overuse according to the ICHD-II criteria.

Exclusion criteria

1. General exclusion criteria:

A. Age under 18 years;

B. Other neurological conditions that may in the opinion of the investigators may interfere with the trial. Any oncological or psychiatric disease, other than the specific types described in the inclusion criteria;

C. Any cognitive disorders and/or behavioural problems which in the opinion of the clinician may interfere with the study;

D. Current abuse of soft drugs or hard drugs or history of abuse of soft drugs or hard drugs in the past 12 months as defined in the DSM-IV criteria under 'Substance abuse' or 'Substance dependence'.(abuse of amphetamines, cocaine, heroin, cannabis);

E. Use of non-triptan or non-analgesic acute anti-headache medication (e.g. ergots, opioids, barbiturates);

F. Pregnancy, planned pregnancy, current nursing. Additionally, all participants will be required to use adequate contraceptive methods;

G. Inability to complete the (electronic) diary in a sensible and accurate manner;

H. Enrolment in other studies that in the opinion of the clinician may confound the results of this study.

2. Btx-specific exclusion criteria:

A. Any motor neuron disorder;

B. Hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation;

C. Infection at the proposed injection site(s);

D. (Suspected) clotting disorder; either of pathological or iatrogenic origin (e.g. caused by marcoumar, sintrom).

3. MRI-specific exclusion criteria:

A. Implanted pacemaker or implanted defibrillator-device;

B. Surgical clips in cerebral vasculature;

C. Metal debris in the eyes;

D. Non-removable hearing-aid;

E. Non-removable neurostimulator;

F. Hydrocephalus-pump;

G. Denture with magnetic fixation;

H. Copper containing Intra-uterine Device;

I. History of surgery in which metal implants were implanted;

J. Weight over 160kg.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-09-2012
Enrollment:	180

Type:	Actual

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion Date:	15-05-2012
Application type:	First submission

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
NTR-new	NL3294
NTR-old	NTR3440
Other	EudraCT : 2011-005124-18
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Study results

Summary results
https://academic.oup.com/brain/article/142/5/1203/5457721