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IIH Provoke: headache mechanisms in idiopathic intracranial hypertension

Submission date
27/09/2022

Recruitment status
No longer recruiting

Registration date
24/10/2022

Overall study status
Completed

Last Edited
01/03/2024

Condition category
Nervous System Diseases

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
idiopathic intracranial hypertension (IIH) is a chronic condition of raised brain pressure occurring in young and often overweight women. Increasing numbers of women are diagnosed with IIH, along with the growing obesity epidemic. Patients can suffer blindness but a frequent debilitating issue is long-term, disabling headaches that diminish the quality of life in affected women. There are currently no specific treatments for IIH headaches, and understanding the underlying causes is limited. Our clinical work suggests that blocking calcitonin gene-related peptide (CGRP), which is a pain chemical, in IIH can improve headaches. Also, our previous research work has shown that glucagon-like peptide-1 receptor agonists can reduce brain pressure.

We aim to explore in detail the role of CGRP in IIH and use detailed physiological assessments in patients to gain an understanding of IIH headaches and potential drug targets. We also aim to evaluate if a glucagon-like peptide-1 receptor agonist alters the provoked headache in IIH by reducing brain pressure. Further, we aim to investigate the impact of exercise, straining and sleep on brain pressure and blood flow.

Who can participate?
Patients aged 18 to 60 years old who are diagnosed with IIH

What does the study involve?
Patients will have a brain pressure monitor inserted where possible. We will explore in detail the role of CGRP by administering this to patients and assessing if it will cause typical IIH headaches. We will be monitoring brain pressure changes and brain blood flow during these IIH headaches. Patients will also receive a glucagon-like peptide-1 receptor agonist to lower the brain pressure after a headache.

What are the possible benefits and risks of participating?
There are potential benefits to involvement including enhanced observation during the trial and opportunities to improve understanding of the condition. The brain pressure monitor allows measurement without further invasive procedures which most IIH patients may require frequently to measure brain pressure. There is a beneficial effect on brain pressure for those

who get a headache provocation and receive the active drug. Also, glucagon-like peptide-1 receptor agonists are known to facilitate weight loss. Furthermore, if a participant suffers a spontaneous headache and attends the research visit, they will benefit from acute in-hospital symptom management.

The major risks in this study relate to the implantable telemetric pressure monitor sensor and the surgical procedure to fit it and to the study medication. There is a small risk from using anesthesia as well as small risks from the procedure of bleeding near the brain, infection or seizures after the procedure. There is a small risk that the device could fail which requires another surgery to remove the device. There are risks of flushing, warm sensation, palpitation and nausea due to the medications. There are rare reports of pancreatitis and low blood pressure associated with the medications.

Where is the study run from?
University of Birmingham (UK)

When is the study starting and how long is it expected to run for?
August 2021 to July 2025

Who is funding the study?
1. Association of British Neurologists (UK)
2. Guarantors of Brain (UK)

Who is the main contact?
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Contact information

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
307968

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 52852, IRAS 307968

Study information

Scientific Title
Mechanisms driving headache in idiopathic intracranial hypertension, a human physiology study

Acronym
IIH Provoke

Study objectives
1. Elevations of intracranial pressure (ICP) in Idiopathic intracranial hypertension (IIH) drive headache signalling through the release of calcitonin gene-related peptide (CGRP).
2. Reducing ICP by targeting the glucagon-like peptide 1 receptor (GLP-1R) signalling pathways alters the headache and cerebrovascular dynamics during a provoked IIH headache.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 27/06/2022, North East - Newcastle & North Tyneside 1 Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, UK; +44 (0)20 7104 8255; newcastlenorthtyneside1.rec@hra.nhs.uk), ref: 22/NE/0081

Study design
Prospective randomized placebo-controlled two-way crossover cohort study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Idiopathic intracranial hypertension

Interventions
IIH Provoke is a prospective, randomised, double-blind, placebo-controlled two-way crossover physiology study. Up to 24 patients with idiopathic intracranial hypertension (IIH) will undergo headache provocation study days. Where possible an intracranial pressure (ICP) monitor will be inserted (unless one previously inserted for clinical reasons).

Participants will be identified at University Hospitals Birmingham NHS Foundation Trust (UHB) within our IIH clinical network during routine clinical appointments by the direct clinical care team. Potential participants will be approached by the direct clinical care team about interest in participating in research after brief eligibility criteria check performed in the clinic or from clinical records and a Patient information sheet will be given or sent out.

Patients will have at least 7 days to consider the study and will be invited for a screening and enrolment visit. Consent will be taken at the beginning of the screening visit. A targeted medical and headache history will be taken along with targeted medical, neuro-ophthalmological assessments. Completion of questionnaires will take place and a headache diary will be dispensed to be completed for the duration of the study. Participants eligible will be enrolled and allocated a study participant identification number (SPIN). Randomisation allocation will take place using this number from the prepopulated computer-generated randomisation list.

If a participant will have an ICP monitor inserted, they will attend for pre-surgical (pre-op) assessment and a surgical visit for the ICP monitor insertion (day-case).

For the main study each participant will be attending for at least 2 research visits. On one visit they will receive a provocation agent: intravenous calcitonin gene-related peptide (CGRP, 30mcg) and on the other visit, a placebo (normal saline). This will be in a random order (cross-over design with randomisation as above). Targeted medical history, headache scores, quality of life questionnaires, ICP and cerebrovascular recordings (where applicable) will be undertaken. Headache diary will be reviewed and new one dispensed if needed.
We will be assessing the effect of the provocation agent on headache, ICP and brain blood flow (where applicable).

If a headache provocation takes place, participants will then receive an ICP lowering agent: Exenatide (20mcg) or a placebo (normal saline) on that day. This will be in random order (cross-over design with randomisation as above). They will attend for one additional visit to receive provocation agent and the alternate ICP lowering agent (assessments as above).

We will be assessing the effect of the ICP lowering agent Exenatide on headache, ICP and brain blood flow (where applicable).

In optional substudies we will be evaluating the effect of straining, exercise, sleep (assessments as above) and investigate for headache biomarkers.

Intervention Type
Other

Primary outcome measure
The following measures were assessed after a single visit:
1. Incidence of provoked headache akin to the participant's typical IIH headache measured using a Headache assessment tool
2. Change in intracranial pressure (ICP) during a headache attack determined using physiological measurement
3. Headache physiological response over the 24 hours post-dose measured using a Headache assessment tool

Secondary outcome measures
The following measures were assessed after a single visit:
1. Change in headache features measured using a Headache assessment tool and diary
2. Dynamic changes in cerebrovascular physiology and headache biomarkers determined using physiological measurement

Overall study start date
01/08/2021

Completion date
31/07/2025

Eligibility

Key inclusion criteria
1. Aged between 18 and 60 years old
2. Previous diagnosis of idiopathic intracranial hypertension (IIH)
3. Able to give informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
60 Years

Sex
Both

Target number of participants
Planned Sample Size: 24; UK Sample Size: 24

Key exclusion criteria
1. Aged less than 18 or older than 60 years old
2. Optic nerve elevation exclusively due to pseudopapilloedema
3. Previous migraine history prior to the diagnosis of IIH (or non-IIH headache) > 1 day per month
4. Pregnant or trying to conceive
5. Significant co-morbidity; such that in the opinion of the investigator it would not be in the participant's best interest to participate in the trial
6. Known cardiovascular or cerebrovascular disease
7. Medication overuse
8. Inability to comply with study schedule or follow-up
9. Currently using Glucagon-like peptide-1 receptor (GLP-1R) agonist or Dipeptidyl-peptidase 4 (DPP-4) inhibitor
10. Contra-indications to undergoing a surgical procedure

Date of first enrolment
13/02/2023

Date of final enrolment
31/05/2025

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
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University of Birmingham

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Sponsor type
University/education

Funder(s)

Funder type
Charity

Funder Name
Association of British Neurologists

Funder Name
Guarantors of Brain

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

Intention to publish date
31/08/2026

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No