HUMAN PHYSIOLOGY OF INTRA-CRANIAL PRESSURE AND THE BIOLOGICAL ROLE OF GLP-1 AGONISTS

BY

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Abstract

Pre-clinical data demonstrates the ability of Exenatide, a GLP-1R agonist, to reduce CSF secretion and intracranial pressure (ICP) in an *in vivo* model. Existing GLP-1R agonists are widely used to treat obesity and diabetes (but do not cause hypoglycaemia).

In the IIH Pressure trial 16 female participants with active idiopathic intracranial hypertension (IIH) were recruited and 15 randomised in a placebo controlled, double-blind trial of Exenatide. Participants were randomised 1:1 to Exenatide (10mcg twice daily sub-cutaneous) or placebo for 12 weeks. Telemetric, intraparenchymal ICP monitors (Raumedic) recorded ICP over 12 weeks. The primary outcomes were ICP at 2.5 hrs, 24 hrs, and 12 weeks.

At baseline BMI was 38.1(6.2) kg/m^2 and ICP 30.6(5.1) cmCSF. ICP, the primary endpoint, fell significantly (2.5 hours -5.7(2.9) cmCSF (p=0.048), 24 hours -6.4 (2.9) cmCSF (p=0.030) and 12 weeks -5.6 (3.0) cmCSF (p=0.058)). Monthly headache days fell in the Exenatide treated cohort (-7.7 (9.2) p=0.069) and vision improved (logMar acuity -0.1 (0.04) p=0.004).

ICP physiology was studied using a standardized protocol. Intracranial pressure (ICP) has been thought to vary diurnally. This study evaluated diurnal ICP measurements and quantifies changes in ICP occurring with changes in body posture in active IIH.

This prospective observational study utilized the IIH pressure cohort prior to randomization. Changes in ICP in the supine position were evaluated. Then, the ICP was measured in the standing, sitting, supine, left lateral decubitus positions and with coughing and bending. Ultimately, changes in ICP over the course of 24 hours were recorded.

15 women were included, mean (standard deviation) age 29.5 (9.5) years, body mass index 38.1 (6.2) kg/m^2, and baseline ICP of 21.2 (4.8) mmHg). ICP rose with the duration in the supine position 1.2 (3.3) mmHg at over 5-minutes (p=0.175), 3.5 (2.8) mmHg over 30-minutes (p=0.0002) and by a further 2.1 (2.2) mmHg over 3 hours (p=0.042). Mean ICP decreased by 51% when moving from the supine position to standing (21.2 (4.8) mmHg to 10.3 (3.7) mmHg respectively, p=0.0001). Mean ICP increased by 13% moving from supine to the left lateral decubitus position (21.2 (4.8) mmHg to 24.0 (3.8) mmHg, p=0.028). There was no significant difference in ICP measurements at any point during the daytime, or between short standing or supine recordings and prolonged daytime and end of night recordings respectively. However, ICP increased progressively in conjunction with lying supine position from 23:00hrs to 07:00hrs by 34% (5.2 (1.9) mmHg, p=0.026).

The IIH Pressure Med study followed, it was a randomised, sequential, open label trial in women with active IIH. Participants were treated for 2 weeks with acetazolamide, amiloride, furosemide, spironolactone and topiramate. Order of treatment was randomised, minimum 1 week drug washout between rounds. ICP was recorded before and after with telemetric, ICP monitors. Cognitive function was tested with the NIH Toolbox Cognition Battery.

14 participants were recruited, at baseline BMI 38.1(6.2) kg/$m^2$and ICP 30.6(5.1) cmCSF. ICP fell significantly with 4 drugs (mean mmHg(SE), p=) acetazolamide -3.31mmHg(0.95), 0.0009, furosemide -3.03(0.88), 0.0011, spironolactone -2.71(0.88), 0.0033, topiramate -2.29(0.85), 0.0095. There was no significant effect between those drugs. Executive function (T Score change(SE), p=) worsened with acetazolamide -10.3(3.2), 0.002 and topiramate -7.0(2.7), 0.012.

IIH Pressure demonstrated that Exenatide reduced ICP acutely and after chronic dosing and improvements in headache and visual function were recorded. GLP-1R agonists represent a new approach to treat IIH. The physiology study demonstrated that ICP does not appear to have a diurnal variation in IIH, but varies by position and duration in that position. ICP rose at night whilst the patient was continuously supine. This knowledge gives reassurance that ICP can be accurately measured and compared at any time of day. The IIH Pressure Med Study assessed Acetazolamide, furosemide, spironolactone and topiramate; all reduced ICP significantly, but there was no statistical difference between any treatment. Cognitive side-effects were common with acetazolamide and topiramate and detailed cognitive assessment demonstrated significantly worse performance following treatment.

Dedications

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Abbreviations and Definitions

Term	Description
ABPI	Association of the British Pharmaceutical Industry
AE	**Adverse Event** - Any untoward medical occurrence in a participant or clinical trial subject participating in the trial which does not necessarily have a causal relationship with the treatment received. Comment: An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.
AR	Adverse Reaction
BCTU	Birmingham Clinical Trials Unit
BD	Bis Die (take twice daily)
cAMP	cyclic Adenosine Monophosphate
CCT	Central Corneal Thickness
CGRP	Calcitonin Gene-Related Peptide
Co-I	Co-Investigator
CNS	Central Nervous System

CRF	Case Report Form
CRN	Clinical Research Network
CSF	Cerebrospinal Fluid
CT	Computerised Tomography
CV	Curriculum Vitae
DEXA	Dual-Energy X-ray Absorptiometry
DPP-4	Dipeptidyl peptidase-4 inhibitor
DVLA	Driver and Vehicle Licensing Agency
GLP-1	Glucagon-Like Peptide 1
GLP-1R	Glucagon-Like Peptide 1 Receptor
GP	General Practitioner
HCG	Human Chorionic Gonadotrophin
HIT-6	Headache Impact Test – 6 items
HRA	Health Research Agency
HVF	Humphrey Visual Fields
ICF	Informed Consent Form
ICP	Intra-Cranial Pressure

IIH	Idiopathic Intracranial Hypertension
IOP	Intra-Ocular Pressure
ISF	Investigator Site File
ITM	Institute of Translational Medicine
LogMAR	Logarithm of the Minimum Angle of Resolution
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NIHR	National Institute for Health Research
NRES	National Research Ethics Service
OCT	Optical Coherence Tomography
OD	Omni Die (take once daily)
PI	Principal Investigator
PIC	Patient Identification Centre
PIS	Patient Information Sheet
PO	Per Os (by mouth)
QoL	Quality of Life

RE	**Related Event** - An event which resulted from the administration of any of the research procedures.
REC	Research Ethics Committee
SAE	**Serious Adverse Event** - An untoward occurrence that: • Results in death • Is life-threatening* • Requires hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly/ birth defect • Or is otherwise considered medically significant by the Investigator** Comments: The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on participants/event outcome or action criteria. * Life threatening in the definition of an SAE refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. ** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or

	may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious
S/C	Subcutaneous (injection route)
SF-36	Short Form - 36 item questionnaire – here taken to mean the RAND version 1
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial
SSCF	Sub-Study Consent Form
UHB	University Hospitals Birmingham NHS Foundation Trust
Unexpected and Related Event	An event which meets the definition of both an Unexpected Event and a Related Event
Unexpected Event	The type of event that is not listed in the protocol as an expected occurrence.
UoB	University of Birmingham
VRS	Verbal Rating Scale

1. Introduction

1.1. General overview

Idiopathic Intracranial Hypertension (IIH) is a disease of raised intracranial pressure with no identifiable cause, the disease primarily affects women of working age, prevalence is increasing and there is no specific licenced treatment for IIH or raised intracranial pressure (ICP) from other causes.

Pre-clinical data demonstrates the ability of Exenatide, a GLP-1R agonist, to reduce CSF secretion and intracranial pressure (ICP) in an *in vivo* model. Existing GLP-1R agonists are widely used to treat obesity and diabetes (but do not cause hypoglycaemia).

This thesis in chapter 2 sets out novel investigation of the physiology of ICP in a cohort of women with active IIH (papilloedema and raised ICP). I investigate ICP physiology with changes in body posture and investigate diurnal variability of ICP in IIH utilising telemetric ICP catheters. The formal study protocol is at section 8.

In chapter 3 I report the findings of the IIH Pressure study investigating the biological effect of Exenatide on ICP. The IIH Pressure study is a randomised, placebo controlled, double blind trial in a cohort of women with active IIH.

In chapter 4 I report the findings of the IIH Pressure Med study, this study is a randomised, sequential, open label trial of five drugs commonly used to treat IIH, acetazolamide, amiloride, furosemide, spironolactone and topiramate.

In chapter 5 I investigate the cognitive effects of drugs in the IIH participant cohort and also investigate the effect of headache on cognitive performance.

1.2. Idiopathic intracranial hypertension

IIH is characterized by increased intracranial pressure (ICP) with no identifiable cause. IIH, also known as pseudotumor cerebri, is a syndrome with the major risk factor of recent weight gain, occurring mainly in overweight women of working age.[1, 2] There is a rising incidence in this disease[3] and the incidence appears related to country specific prevalence of obesity.[4]

1.2.1. IIH Symptoms

In the majority of those presenting with IIH they will have headache that is progressively more severe and frequent, with a divergence of traditional considerations of a raised intracranial pressure headache[5] to a phenotype that is highly variable and commonly mimics migraine.[6, 7] Other reported symptoms include transient visual obscurations (unilateral or bilateral darkening of the vision typically lasting seconds), pulsatile tinnitus, back pain, dizziness, neck pain, visual blurring, cognitive disturbances, radicular pain and horizontal diplopia.[2, 8, 9] Prognosis is variable as IIH can either be self-limited or have a lifelong chronic course with significant effects on quality of life.[10, 11]

1.2.2. IIH Management

In 2018, the first consensus IIH guidance was published.[1] The document was reviewed by a committee of international key opinion leaders and a patient group which established a James Lind Alliance Priority Setting Partnership for adult IIH.[12] It set out key diagnostic and management principles. The diagnostic principles of the investigation of papilloedema are to find any underlying treatable cause in a timely manner, protect the vision and ensure timely re-examination when vision is at risk, and to enable onward care of the patient with the input from the most appropriate

experienced clinician. Key considerations are to exclude secondary causes such as venous sinus thrombosis with appropriate imaging and check blood pressure to exclude malignant hypertension.

1.2.3. IIH Diagnosis

The Friedman et al.[13] 2013 diagnostic criteria are used although a key area of uncertainty still exists with the diagnostic cut-off, lumbar puncture opening pressure (LP OP) 25cm CSF as was then recognised. A grey zone between 25 and 30cmCSF exists with the recommendation that where measured LP OP does not fit the clinical picture consideration should be given to repeat measurement or intracranial pressure monitoring.

1.2.4. IIH Treatment

The key management principles are addressing the underlying modifiable risk factor of weight gain; protecting the vision through regular assessment and escalation of treatment when sight is threatened; and reducing headache morbidity through active management. Importantly considerations included the indication for CSF diversion surgery in declining visual function. However alternative interventions such as neurovascular stenting do not yet have evidence to recommend them. It should also be stressed that headache alone is not an indication for CSF diversion with a majority of patients having persistent headache following the procedure.[14]

The major achievement of this document is the interdisciplinary working to provide a framework to standardise care for those with IIH. This standardised approach to care has been subsequently

published in the European Headache Federation Guidelines for IIH.[15] Drug treatment is discussed in section 1.4.

1.3. Intracranial pressure monitoring

1.3.1. Overview

The most common method of ICP measurement in IIH remains lumbar puncture, with several well documented negative aspects.[16] Direct measurement of intracranial pressure (ICP) is either non-invasive (yet to be used routinely) or invasive. Invasive ICP measurement can be performed at various anatomical sites namely intra-ventricular, intra-parenchymal, sub-arachnoid, sub-dural, epidural; where there is CSF communication ICP can be measured by lumbar puncture.[17] Basic ICP measurement by external ventricular, lumbar drains or lumbar puncture is made by fluid column; more recently a variety of micro-sensors have become available that locate in the target tissue. These have been limited by drift phenomena and the requirement for external wiring, thus the risk of infection with use in excess of 72hrs.

1.3.2. Telemetric pressure monitoring

Telemetric intracranial pressure monitors are increasingly being used clinically and for research.[18] They provide many advantages particularly allowing frequent and accurate monitoring of pressure, which is non-invasive following initial implantation. The telemetric probes are inserted surgically under local or general anaesthesia via a burr-hole with placement of the probe into the brain parenchyma of the right frontal lobe. The safety profile has been established.[18, 19] The risks are minimal and relate to the surgical procedure itself; of note however is driving status. Currently patients need to desist from driving and inform the DVLA once a monitor is placed and request permission to resume driving, a process that can take some weeks. Rarely telemeters can fail in use, in this instance replacement would be necessary involving a further surgical procedure if the participant agreed.

Telemetric ICP monitors are now available commercially. There are 2 main systems, Neurovent p-Tel™, Raumedic, Helmbrechts, Germany and Sensor Reservoir, Miethke™, Potsdam, Germany. The wiring issue is resolved with wireless power and reading utilising induction technology. The drift issue is solved in both systems by way of an external monitor reading atmospheric pressure and solid-state sensor technology. The 2 systems differ with Neurovent™ p-Tel siting a pressure sensor in the brain parenchyma; meanwhile the Miethke™ system is based on a sensor within a reservoir attached to a ventricular drain. Both devices are readable by external hand-held equipment, both devices are passive in the sense that they have no power or memory integral to the device and so pressure is only recorded with the external equipment in-situ.

The major initial application for the Miethke™ system is in refining valve settings in challenging patients, a recent case series highlights this application, of note the highest frequency of valve adjustments was seen in the IIH cohort.[20]

More data is available for the Raumedic™ p-Tel as it has been available for longer. It sites a solid-state pressure sensor approx. 20mm into the brain parenchyma, usually within the right frontal lobe. From the largest published series there is a low complication rate, approximately 6% overall, with seizures affecting 3% and infection in 1.5%;[21] however, this was in a series of patients with significant structural brain abnormality (for example hydrocephalus) and the rate of such complications is likely lower in IIH patients. Of note, the UK driving regulations allow resumption of driving 1 week after insertion in patients without complications. The device provides a high degree of accuracy with low drift.[19, 22] Many have been kept in situ beyond the licensed 3 month period;[21,

23] where they have been shown to retain their accuracy with low drift of 2.5mmHg over a median 241 day implantation period. The device samples at 5 Hz, considerably lower than the wired and Miethke™ systems, although this is sufficient for waveform analysis.[18, 19] The device is capable of long-term recordings for up to 1 week with the present hardware and can be worn by an ambulant patient out with the hospital environment.[18]

Telemetric ICP monitors have an evolving role in diagnosis and monitoring of several conditions. In IIH, particular roles could include evaluating whether neurosurgical shunt placement is advised in a deteriorating patient developing fulminant disease. Furthermore, it is useful in evaluating whether pressure is pathologically elevated in those with minimal ocular features and in shunted patients. Monitors can inform the setting of CSF shunt valves aiming to abrogate low pressure headaches, at present seen in 23%.[14] ICP telemetry may also facilitate the differentiation between raised pressure headaches and migrainous headaches.[18]

1.4. ICP physiology in IIH

ICP varies throughout the day in tandem with posture but might also vary due to a wide variety of other variables. No previous studies have investigated the physiological characteristics of ICP in a cohort of patients with IIH.

Establishment of raised ICP is a key clinical criterion of the diagnosis of IIH, in clinical practise this is usually achieved by lumbar puncture, though increasing use is being made of invasive ICP measurement in some circumstances. Lumbar puncture can be challenging in this cohort owing to body habitus and provides limited information. Only a single ICP measurement is recorded by visual inspection of a manometer during the procedure. ICP is by necessity recorded in the left lateral position, although previous work has attempted to relate pressure recorded in this position to those sitting without success.[24] Currently sitting ICP is not used in clinical practice.

Previous work has established an ICP cut-off at 25cmCSF for diagnosis of IIH, [25] which is used in current guidelines[1, 13] though there remains uncertainty regarding the validity of the cut-off measured at a single timepoint, as the natural history of ICP in IIH is unknown.[26]

Determining change in ICP after adopting a posture is critical, as a defined protocol for measuring ICP has not yet been widely established in clinical practice. In previous work detailing the effects of posture changes in a cohort of patients with raised intracranial pressure due to heterogenous pathologies, *Andresen et al.* utilised median pressure over a 10-minute interval following each posture change after an unspecified time period to allow the ICP to stabilise. [27]

1.4.1. Positional ICP

Andresen et al. previously observed that ICP measurement in the left lateral position presents a distorted view of the ICP state of a patient being elevated above the supine posture.[27] Detailed work by *Pedersen et al.* has gone on to show that the measurement of ICP in the left lateral position is fraught, with small changes in posture of the neck and hips having marked effects on the recorded ICP.[28] Although guidelines state that ICP should be measured with hips flexed to 90° [13] the frequent difficulty of performing the procedure in this cohort, given the phenotype of abdominal adiposity which can limit hip flexion, highlights the need to reconsider the optimal position for standardised ICP measurement in IIH.

The lumbar puncture will remain the mainstay of ICP measurement for most patients, and its drawbacks are already recognised in current guidelines.[1] The increasing utility of invasive ICP measurement demonstrates a need for parallel diagnostic ICP criteria based on representative postures, most likely supine.

1.4.2. Normal ICP

The challenge of attaining normative ICP measures will remain, owing to the ethical problems in subjecting healthy volunteers and patients to more invasive procedures. However, efforts have recently been made utilising pseudo-normal populations. *Andresen et al.* reported ICP in 4 patients following removal of well demarcated brain tumours [29] and *Petersen et al.* reported ICP readings in 9 "*as normal as possible*" patients who following investigation were found to have no neurosurgical problem.[30] Most recently *Norager et al.* have reported a systematic review aiming to establish normative cut-offs for both lumbar CSF pressure and supine ICP. [31]

1.4.3. ICP diurnal variability

A widely held belief in international literature is that ICP varies diurnally.[1] This may relate to differences observed between sleep and daytime recording which are naturally in different postures, and between supine and erect postures respectively. The phenomenon has not yet been studied sufficiently.

1.4.4. Sleep and ICP

There are previous studies of ICP during sleep. *Ogashiwa et al*. reported a series of patients undergoing monitoring post-operatively for a variety of indications including normal pressure hydrocephalus.[32] *Riedel et al*. reports the observation of B-waves in patients undergoing monitoring and sleep studies following aneurysm closure with the finding of B-waves associated with sleep-related breathing disturbance.[33] *Chari et al.* present a large series in patients with hydrodynamic disturbances stratified into day and night recordings[34] and *Langvatn et al.* investigated a series of children with cranial syntosis.[35] The only study reporting analysis of ICP over sleep was *Ogashiwa et al.* in a single case of a patient with Chiari malformation where pressure was observed to rise until a newly inserted shunt valve opened dropping pressure.[32] The interpretation of the above studies is limited by the limitations in the number of patients, length and nature of recording and heterogeneity of the diseases and circumstances of the studies. Obstructive Sleep apnoea is a condition commonly encountered in patients with IIH and it is thought to have a relationship with variability of ICP overnight, however this has not been studied to date.

Early morning headache is a classical feature of IIH and may be indicative of the higher ICP following sleep, anecdotally many IIH patients report sleeping sat up to mitigate early morning headache.

Furthermore, in patients following a normal day-night routine the night-time period in a recumbent position represents the longest period of exposure to highest ICP, thus nocturnal elevated and rising ICP may play a significant role in the disease pathology. This could also provide opportunity for intervention with tailoring treatment to preferentially reduce nocturnal ICP.

1.5. CSF Physiology

1.5.1. CSF Secretion

The choroid plexus is the principal site of CSF production; this is driven by the net movement of sodium ions (Na^+) from the blood to the cerebral ventricles, creating an osmotic gradient down which water moves. Although several channels are involved in this process, the principal channel is the Na^+ and K^+ dependent adenosine triphosphatase (Na^+/K^+/ATPase) that actively transports Na^+ into the cerebral ventricle and is the rate-limiting step. [36, 37] The other principal channels involved in CSF secretion are NKCC1 and the HCO_3^- , however the relative contributions of these transporters is unclear.[38]

The water channel AQP1 is expressed on the luminal surface of the choroid plexus.[39, 40] It has a significant role in the osmotic permeability of the membrane, however CSF secretion is only reduced by 20% in mice deficient in AQP1[41] and humans deficient in functional AQP1 are neurologically normal.[42] This is a subject of ongoing work and the relative contributions of water channels are not yet resolved.[43]

1.5.2. CSF Mechanics

The central nervous system is surrounded by CSF, which also fills and communicates with the ventricular system and sub-arachnoid space. It has a water-like density and viscosity, and has a lower protein content than that plasma.[44] CSF is not static, but rather demonstrates pulsation throughout the ventricular system. Imaging studies demonstrate that this pulsation follows the cardiac cycle.[45] CSF flows caudally in systole with flow reversal in diastole without net flux. There is

marked pulsatility at the aqueduct.[46] CSF secretion occurs within this but the relative volumes mean there is no appreciable impact on the beat-to-beat CSF pulsation.

1.5.3. Glymphatics

In addition to its mechanical property in maintaining pressure homeostasis within the brain CSF has a role in 'waste' clearance from the brain parenchyma. The detail of this system has recently started to be uncovered with discovery of the glymphatic system[47, 48] and connection to the lymphatic system proper via meninges and blood vessels and nerves exiting the cranium.[49-51]

Rodent work has suggested a 3-step process regarding glymphatic function. Firstly, CSF is transported from the basal cisterns to the subarachnoid space overlying the cerebral hemispheres, due to bulk flow, where it enters the periarterial spaces. Secondly CSF is then propelled from the periarterial space to the interstitial space in a process facilitated by the AQP4 channels on astroglial end-feet. Finally, the mixed CSF/interstitial fluid is transported to the perivenous compartment of large cerebral veins exiting into lymphatic vessels proper and then then systemic circulation. [47] [52]

1.6. Existing IIH Treatments

There are several medications presently used for IIH, there is only some class one evidence of efficacy for acetazolamide[53, 54] and minimal *in vitro*, *in vivo* or clinical evidence for other drugs in current use including topiramate, furosemide, amiloride and spironolactone. All of which are thought to principally reduce ICP through reduced CSF secretion. There are no studies available presently to guide the choice of these drugs in individual patients. The common existing drugs used in IIH have been evaluated acutely in vivo at clinically relevant doses, and were not found to significantly reduce ICP, with the exception of topiramate.[55] Existing treatments for IIH also include weight management, low calorie diet has been shown to improve visual markers of IIH and recently the IIH Weight trial established the efficacy of bariatric surgery over a community weight loss programme in the treatment of IIH.[56, 57]

Disordered CSF dynamics have been suspected to underlie the raised ICP seen in IIH. There are currently no novel drugs targeting the underlying pathogenesis driving IIH, which remains elusive. Novel therapies are currently focussed on reducing ICP through reducing CSF secretion. Ideally novel therapies would also reduce weight as this approach is disease modifying in IIH.[56]

1.6.1. Acetazolamide

Acetazolamide, a carbonic anhydrase inhibitor, is the longest established and main pharmacological therapy used in IIH. Class I evidence exists for its use in IIH, and two RCTs have examined its efficacy [53, 54]. In 2014, a large randomised double-blind placebo-controlled study of acetazolamide combined with a low-sodium diet was published[53]. The IIH Treatment Trial (IIHTT) assessed ICP at baseline and 6 months with lumbar puncture, the study demonstrated a mean difference of -59.9

mmH_2O (-96.6 to -23.4) (95% confidence interval) favouring the acetazolamide group by 6-months. Whilst there were limitations on the reporting of the ICP data (only 85 participants agreed to lumbar puncture at 6 months and the analysis utilised multiple imputation to account for missing data) it recognises that reduction of ICP is key for disease remission. Of note there was no effect of acetazolamide on headache seen in the IIHTT.[7] High doses of acetazolamide were used in the IIHTT, with more than 40% of patients treated with 4000mg of acetazolamide daily. This dose may not be tolerable in a real-world setting, as previous studies have demonstrated that 48% of patients discontinue acetazolamide when daily doses of 1500mg are used. [54] In 2015, following the publication of the first two randomised control trials for medical treatment in IIH,[8, 54] an updated Cochrane review highlighted that there was insufficient evidence to recommend or reject the efficacy of acetazolamide for treating IIH and insufficient evidence for other drugs used in IIH.[58]

1.6.2. Amiloride

Amiloride is a potassium sparing diuretic, it has been shown to reduce ICP in animal models via blockade of the Na+/H+ exchanger or Na+ channels,[59, 60] but there have not been any human studies thus far investigating its effect on ICP, although use in IIH is reported in a case series.[61]

1.6.3. Furosemide

Furosemide, a loop diuretic, has been used to treat IIH,[62] although there is evidence for reduction of ICP in other diseases in humans,[63] it has not previously been evaluated within a trial setting in IIH.

1.6.4. Spironolactone

Spironolactone is also a potassium sparing diuretic commonly used in the settings of heart failure and hypertension. A study by Friedman et al. in 1998 assessed the effect of spironolactone along with chlorthalidone and sympathomimetic therapy on orthostatic oedema in IIH and matched control groups.[64] However the study was unable to formally assess clinically relevant outcomes or ICP. Additionally, spironolactone has been observed to control IIH symptoms in patients with IIH and primary aldosteronism in a case series.[61]

1.6.5. Topiramate

Topiramate is a sulfamate modified fructose diacetonide, originally developed as an anticonvulsant drug for the treatment of epilepsy. However, it has also been used for the treatment of migraine and for weight loss. Topiramate has several cellular targets including voltage gated sodium channels, GABA-A receptors, and carbonic anhydrase. It has similar inhibitory activity to acetazolamide of the Carbonic Anhydrase II and XII isoforms.[65]

Topiramate has class 1 evidence as prophylaxis in the treatment of migraine.[66-68] It also has well documented effects on weight loss.[69, 70] With weight loss known to be beneficial in the treatment of IIH[56] and headache one of the leading causes of morbidity in IIH, topiramate is of particular interest as a potential therapy. A 2007 trial reported by *Celebisoy et al.* randomised 40 patients with IIH to treatment with topiramate or acetazolamide, they found significant improvements in visual fields in both groups, and no significant difference in treatment efficacy between the groups.[71]

1.6.6. Bendroflumethiazide

Bendroflumethiazide is a thiazide diuretic, it has wide ranging clinical use, most commonly in the setting of hypertension and acts on the sodium – chloride co-transporter. It is used clinically in IIH,[72] though there is no clinical trial evidence supporting its use. There is a small amount of evidence regarding the related drugs chlorthalidone and hydroflumethiazide, a case series, Jefferson and Clark 1976, reported improvements in visual measures in an IIH cohort with both drugs.[73] A subsequent study by Friedman and Streeten 1998, utilised chlorthalidone and spironolactone in combination with other therapies; out of 30 patients 4 had improvement in papilloedema and 7 in headache measures. [64]

1.6.7. Surgical management

There are also developments with surgical management of IIH, two trials are currently ongoing, the IIH Weight Trial[74] (ClinicalTrials.gov Identifier: NCT02124486) is a randomised controlled trial of Bariatric Surgery Versus a Community Weight Loss Programme and opened to recruitment in 2014, the initial results demonstrate efficacy of bariatric surgery over community weight loss.[57] The SIGHT trial (ClinicalTrials.gov Identifier: NCT03501966) opened in 2018 and is a triple arm randomised controlled trial of medical therapy (acetazolamide) vs. medical therapy with Optic Nerve Sheath Fenestration vs. medical therapy with Ventriculo-Peritoneal Shunting.

1.7. Novel IIH Treatments

1.7.1. 11ß-hydroxysteroid dehydrogenase type 1

11ß-hydroxysteroid dehydrogenase type 1 (11ß-HSD1) is an intracellular enzyme that converts inactive cortisone to the active cortisol. This amplifies local glucocorticoid activity independent of systemic cortisol. 11ß-HSD1 expression and activity has been demonstrated in choroid plexus epithelial cells, along with other key elements of the glucocorticoid signalling pathway.[75, 76] Inhibitors have been developed, including AZD4017, originally as potential therapies for diabetes mellitus type 2 and the metabolic syndrome. Glucocorticoid metabolism has been characterised in IIH in relation to therapeutic weight reduction; global 11ß-HSD1 activity decreased with weight loss as measured by urinary glucocorticoid metabolites by gas chromatography/mass spectroscopy.[76] Importantly it was noted that the reduction in ICP significantly correlated with reduction in 11ß-HSD1 activity.[76] Of interest is that 11ß-HSD1 inhibition reduced intraocular pressure and it has been shown that secretory mechanisms of the ocular ciliary body are akin to that of choroid plexus epithelium.[75-77]

11ß-HSD1 inhibitors do not affect systemic glucocorticoid metabolism,[78] but would reduce CSF secretion though reducing local cortisol availability in the choroid plexus with subsequent reduction of downstream glucocorticoid receptor mediated sodium transportation, reduced osmotic gradient and decreased water movement into the cerebral ventricle. .[75, 76] Conversely systemic administration of glucocorticoids has been found to precipitate intracranial hypertension.[79] The IIH Drug trial (IIHDT), clinicaltrials.gov identifier NCT02017444, has investigated the ability of an 11ß-HSD1 inhibitor to reduce CSF secretion and hence ICP in patients with IIH.[80] IIHDT is the first phase 2 double blind placebo-controlled trial in IIH.

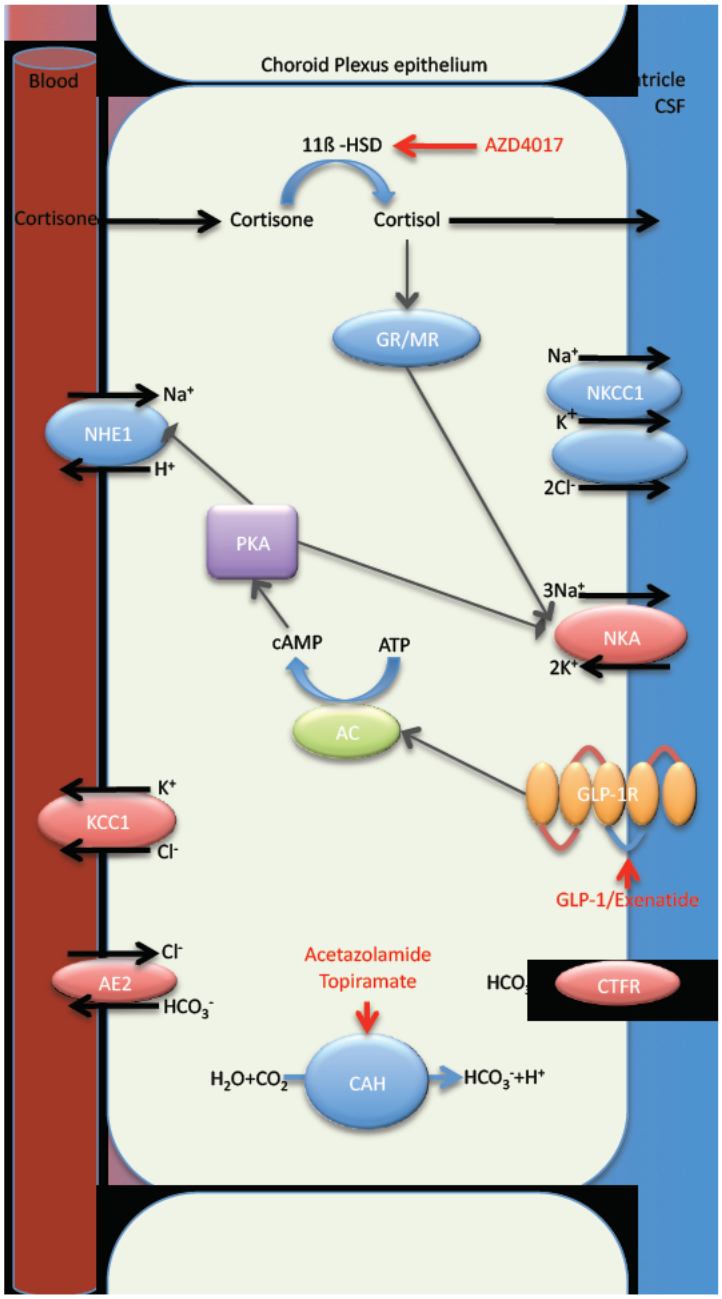


FIGURE 1 - DRUG SITES OF ACTION IN THE CHOROID PLEXUS

The major Ion channels responsible for CSF secretion in the choroid plexus are shown with sites of action of acetazolamide, AZD4017 and exenatide. Cortisone is converted to the active cortisol by 11ß-HSD1, Cortisol binds to the GR and MR receptors which upregulate Na^+ K^+ ATPase activity; AZD4017 inhibits 11ß-HSD1 reducing local availability of cortisol. Exenatide binds and activates GLP-1R stimulating the conversion of ATP to cAMP by AC. cAMP activates PKA which inhibits the Na^+ H^+ exchanger reducing Na^+ re-absorption and also inhibits the Na^+ K^+ ATPase reducing Na^+ excretion. Carbonic anhydrase catalyses the conversion of H_2O and CO_2 to H^+ and HCO_3^- which is important in the establishment of the osmotic gradient. Both acetazolamide and topiramate inhibit carbonic anhydrase function.

11ß-HSD: 11ß-hydroxysteroid dehydrogenase type 1, GR/MR: Glucocorticoid and mineralocorticoid receptors, NKCC1: Na-K-Cl cotransporter, NKA: N-K ATPase, PKA: protein kinase A, NHE1: Na-H anti-porter, ATP: adenosine triphosphate, cAMP: cyclic adenosine monophosphate AC: adenylate cyclase, GLP-1R: Glucagon-like peptide 1

receptor, GLP-1: Glucagon-like peptide 1, CTFR: cystic fibrosis transmembrane conductance regulator AE2: anion exchange protein 2 KCC1: K-Cl cotransporter 1

1.8. GLP-1 agonists

Gut neuropeptides are increasingly being recognised for their role in the central nervous system (CNS). A principal gut neuropeptide is glucagon like peptide -1 (GLP-1) predominantly secreted from the distal small intestine in response to a meal.[81] GLP-1 is principally known to stimulate insulin release, proliferation of pancreatic beta cells and reduces blood glucose in diabetics.[82] GLP-1 stimulates glucose dependant insulin secretion and inhibits glucagon release, lowering blood glucose only in the presence of insulin and not resulting in hypoglycaemia.[82] GLP-1 is also synthesised in neurons of the nucleus tractus solaris that project to the hypothalamus[83] and promotes satiety and weight loss.[84]

Within the brain, GLP-1 signals centrally mainly through GLP-1Receptor (GLP-1R), a G-coupled protein receptor expressed in selected cell types within the pituitary gland, hypothalamus, hippocampus, olfactory cortex, circumventricular organs and interestingly the choroid plexus.[85] GLP-1 crosses the blood brain barrier,[86] and can be detected in the cerebrospinal fluid.[87] However, the pathways by which gut secreted GLP-1 exerts central effects are debated: 1) binding to vagal afferents, or 2) via the blood brain barrier.[88] The vagus nerve can also stimulate GLP-1 production at the nucleus tractus solitarius with a dense and widespread network of GLP-1 fibres reaching the ventricles and CSF.[83]

In additional to the role in regulating glycaemia GLP-1 has been shown to have actions in the CNS. GLP-1 is involved in regulating satiety and weight through signalling at the hypothalamus.[89] Interestingly, meal stimulated levels of GLP-1 are lower in obese patients.[90] GLP-1 agonists are used therapeutically to promote weight loss.[89] GLP-1 has also been shown to have anti-

inflammatory effects and potentially neuroprotective properties in *in-vitro* and *in-vivo* models of Parkinson's and Alzheimer's disease.[91]

There is also growing evidence that GLP-1 may have a role in fluid secretion. In the renal proximal tubule GLP-1 acts to reduce sodium resorption and promote diuresis.[92, 93]

The choroid plexus is the fluid secreting structure within the brain producing the majority of the cerebral spinal fluid (CSF). The structure of the choroid plexus epithelial cells is analogous to an inverted renal proximal tubule with a similar mechanism of fluid secretion and hence GLP-1 may also reduce CSF secretion in the brain. GLP-1 also has a diuretic effect by reducing Na^+ re-absorption in the renal proximal tubule, thereby increasing Na^+ and water excretion.[94] Activation of GLP-1R stimulates the conversion of adenosine triphosphate to cyclic adenosine monophosphate (cAMP) by adenylate cyclase. cAMP activates protein kinase A which inhibits the Na^+ H^+ exchanger, thus reducing Na^+ re-absorption. Choroid plexus epithelial cell function is inverted compared to renal proximal tubule but with an analogous fluid transport mechanism,[95] and as such GLP-1R was investigated as a potential target for conditions with raised ICP. It has been shown that GLP-1 receptor (GLP-1R) is expressed in the human choroid plexus.[96]

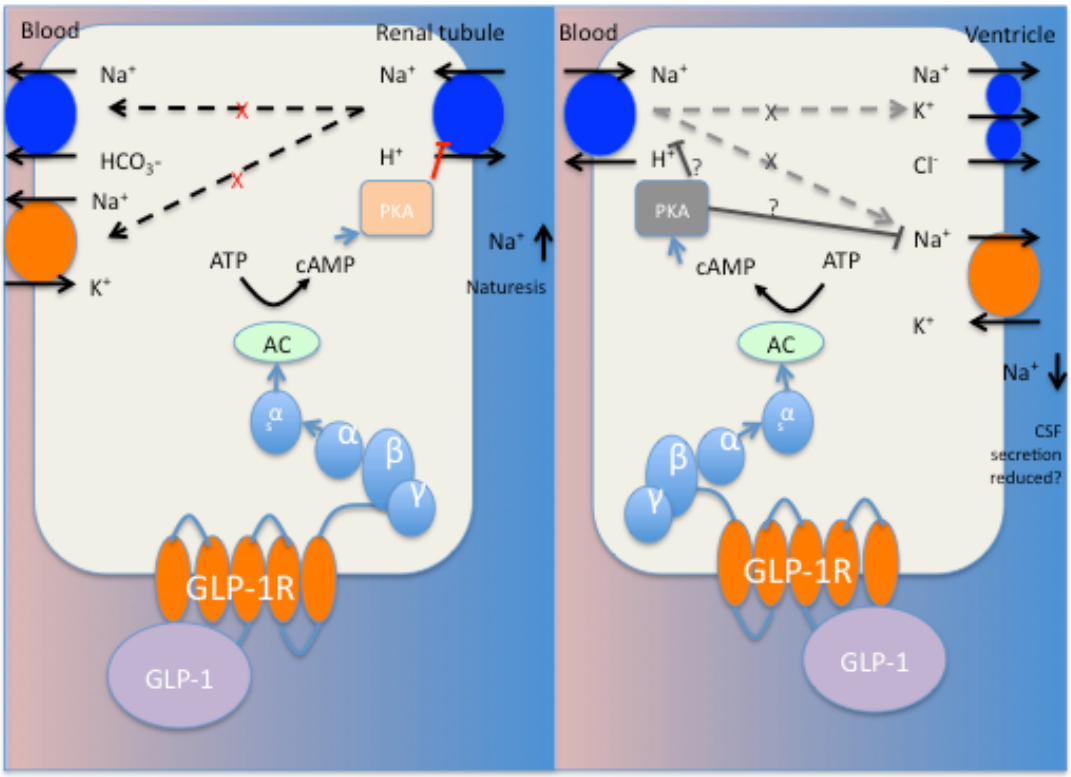
Preliminary work explored the impact of gut neuropeptides in vitro and in vivo.[96] These data suggest that at the choroid plexus contains GLP-1 receptors which are upregulated when activated by a GLP-1 agonist. Additionally in vitro assays of CSF secretion are inhibited by GLP-1 through a cAMP/protein kinase A dependent pathway. GLP-1 also regulates fluid dynamics and reduces intracranial pressure in the rodent. Treatment with the agonist exendin-4 modulates the GLP-1R in

the rat choroid plexus through agonist induced receptor internalisation, which was shown to increase cAMP generation and reduce Na^+/K^+/ATPase activity. Importantly exendin-4 reduced ICP in conscious rats at clinically relevant doses. There was a 65% reduction in ICP 30 minutes post dose compared to baseline and a cumulative effect seen with reduction in the ICP to 79.3% and 72.5% of baseline values pre-dose at days 2 and 4 respectively of the experiment. The action was blocked by intraventricular administration of the GLP-1R antagonist exendin 9-39, suggesting the effect is mediated by the GLP-1R in the brain. Importantly, the effect was also seen in a rat model with markedly raised ICP.[96]

GLP-1 analogues have a clinical role in the management of type 2 diabetes mellitus, as well as for weight loss in obesity. Several GLP-1 agonists have been developed and are now licensed drugs.[97] These include exenatide twice daily, exenatide once weekly, liraglutide, lixisenatide, albiglutide, dulaglutide and most recently semaglutide. Currently only liraglutide is licensed for weight loss in obesity. They vary in structure and pharmacology, ability to penetrate the blood brain barrier (BBB) as evidenced by CNS effects. Importantly the choroid plexus epithelium lies outside the BBB.[98] Exenatide has been shown to induce changes in fat distribution in a diabetic population.[99]

The IIH Pressure study evaluated the effects of the GLP-1 agonist Exenatide on CNS fluid secretion in patients with idiopathic intracranial hypertension (IIH). Patients with IIH are an ideal population in which to study the CNS effects of gut neuropeptides as patients are typically obese with evidence of central adipokine dysregulation.[100] Patients also have elevated ICP.[101] Effects of GLP-1 on fluid secretion at the choroid plexus are reflected in alterations in ICP which can be evaluated though telemetric intracranial pressure monitoring.

FIGURE 2 - GLP-1 ROLE IN CPE.



GLP-1 role in CPe. *The binding of a GLP-1R agonist to its receptor on proximal tubule epithelial cells stimulates the conversion of ATP to cAMP by adenylate cyclase. camp activates protein kinase A (PKA), which phosphorylates the Na+/H+ exchanger resulting in its inhibition, thus preventing Na+ reabsorption into the bloodstream. Panel B. CSF secretion by CPe cells is regulated by ion channels similar to those in the renal proximal tubule. We propose that GLP-1R agonists may modulate sodium movement in the choroid*

plexus and reducing CSF production. Abbreviations: AC – adenylate cyclase ATP - adenosine triphosphate, AQP1 – aquaporin 1, αs –alpha stimulatory subunit, β - beta subunit, cAMP – cyclic adenosine monophosphate, GLP-1 – glucagon like peptide 1, GLP-1R – glucagon like peptide 1 receptor, γ - gamma subunit, PKA – protein kinase A

1.9. Optical Coherence Tomography

Visual monitoring of patients is a key principle of management,[1] in addition to visual field perimetry, Optical Coherence Tomography (OCT) has allowed new observations in papilloedema. OCT is a rapid, reliable, reproducible and non-invasive imaging technique, using reflected light waves to produce high-resolution cross-sectional and 3D representations of retinal structures. Optic Nerve Head (ONH) OCT measures have been correlated with the modified Frisén grading of papilloedema.[102, 103] The non-invasive nature of these techniques make them ideal in follow-up in contrast to lumbar puncture which is feared by patients.[16]

When investigating papilloedema OCT is useful in the differentiation of pseudo-papilloedema from true papilloedema, a key area of misdiagnosis.[104, 105] Combining blue auto-fluorescence and disc volume OCT scanning can highlight buried crystalline drusen clearly. Peripapillary hyper-reflective mass-like structures, termed PHOMS,[106, 107] may be nerve fibre in origin.[106] Further work may define their significance.

Standard measurements for papilloedema include peripapillary retinal nerve fibre layer (pRNFL) and ONH volume. These are reliably increased in active IIH compared to controls, are significantly associated with CSF opening pressure and improve following treatment.[108] OCT has revealed dynamic deformation of the peripapillary retinal pigment epithelium and Bruch's membrane (pRPE/BM) regressing towards the normal shape with reduction of ICP.[109, 110] Deformation in pRPE/BM may be of particular value in evaluating atrophic papilloedema with minimal RNFL swelling, as deflection of pRPE/BM may correlate with disease activity. Macular RNFL thickness has been

shown to be significantly reduced compared to controls, reduces over time and is associated with ONH volume measurements at baseline and visual function.[111, 112]

1.10. Cognitive

IIH is a chronic, relapsing disease characterised by raised ICP. There are a number of common disease manifestations including headache, papilloedema and visual disturbance. Patients also report cognitive fogging, this has been assessed in several small studies.

Cognition is impaired in many neurological disorders and also in other medical conditions such as chronic pain states. Patients with IIH are known to have high incidence of depression and anxiety[113] but there have been few studies investigating cognition. A mild general intellectual impairment, particularly affecting verbal testing was found by Sorensen et al.[114] these abnormalities improved following retesting after treatment. Kharkar et al.[115] reported a wider range of impairment in a small retrospective study of IIH patients with deficit noted particularly in learning and memory domains.

Yri et al.[116] conducted an unblended prospective study in a series of patients with newly diagnosed IIH. Participants were followed up at 3 months. They found deficits in reaction time, processing speed, visuospatial memory, and attention; these were fairly marked and were of the order of those found in schizophrenia at presentation. In their series these deficits did not improve substantially over the course of three months despite improvement in ICP and headache scores.

To date only a single study has investigated the efficacy of a therapeutic intervention on cognitive performance in IIH.[57] The IIH Weight Trial (IIHWT) was a randomised controlled trial of bariatric surgery vs community weight loss in a cohort of women with IIH. An obese control group without IIH allowed baseline comparison between IIH and obesity. *Grech et al.*[117] demonstrated impaired

executive function, using a bespoke battery of cognitive tests, in IIH compared to controls. They also demonstrated reversibility of cognitive impairment with decreased intra-cranial pressure. In that study cognition was also influenced by headache severity, depression and sleep apnoea.

The effects of drug treatment on cognition in IIH have not previously been assessed. Acetazolamide is the commonest drug treatment for IIH. Cognitive impairment is reported in patients taking this drug when it has been assessed in the setting of acute mountain sickness. Wang et al. demonstrated that despite improvements in acute mountain sickness volunteers administered acetazolamide had impaired attention, processing speed, reaction time, short-term memory, and working memory after rapid ascent compared to placebo.[118]

Topiramate is increasingly used for the treatment of IIH. Topiramate has class 1 evidence as prophylaxis in the treatment of migraine.[66-68] It also has well documented effects on weight loss.[69, 70] With the beneficial effect of weight loss in IIH[56] and headache one of the leading causes of morbidity in IIH, topiramate is of particular interest as a potential therapy. A 2007 trial reported by Celebisoy et al. randomised 40 patients with IIH to treatment with topiramate or acetazolamide, they found significant improvements in visual fields in both groups and no significant difference in treatment efficacy between the groups.[71] However topiramate commonly causes cognitive impairment with deficits in many domains including verbal fluency, executive function and working memory.[119, 120]

Headache has been shown to affect cognitive performance with several studies confirming impairment during migraine attacks.[121-125] The IIHWT reported deficits in attention correlated with headache severity in IIH patients.[117]

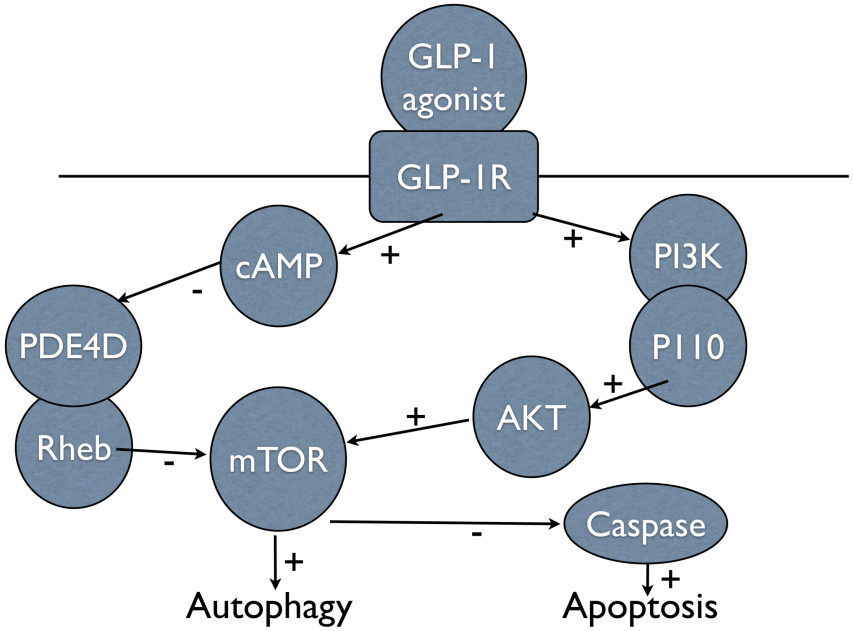
1.11. Neuroprotection

Neuroprotection refers to mechanisms or strategies used to protect against injury or degeneration in neurological insults or disease. Neuro-protective effects of GLP-1 agonists have been demonstrated experimentally in animal models of conditions including Alzheimer's, Parkinson's disease and ischemic stroke.[91] Additionally GLP-1 neuro-protection has been suggested in animal models of both mild, and moderate/severe TBI. These studies showed that GLP-1 analogues administered by either infusion or via transfected mesenchymal stem cells protected animals from injury in models of TBI either measured by cognitive outcome but also via reduced cell loss in the hippocampus and reduced neuronal and glial abnormalities in the cortex.[126-129] The mechanism of action was not investigated but these studies support a neuroprotective role for GLP-1 post TBI.

Recent studies suggest that the mechanism by which GLP-1 exerts potential neuro-protective actions is through up-regulation of cAMP and activation of mammalian Target of Rapamycin (mTOR).[130] mTOR is a serine/threonine kinase which has an important role in energy handling pathways in cells and regulates cell growth, proliferation, motility, survival, protein synthesis and transcription. mTOR activity influences cell survival following injury, including TBI models[131] and also potential regeneration in many tissue and animal models. Interestingly both up-regulation and down regulation of mTOR have been shown to have neuro-protective effects in animal models of stroke; this may be related to the balance of apoptosis, autophagy and cell survival at different time-points after injury. GLP-1 is protective of pancreatic islet cells in a model of glucose activity and this effect is reversed by administration of rapamycin, a specific mTOR inhibitor.[132] This has also been shown in a model of neuro-protection using the PC12 (rat phaeochromocytoma) cell line and methylglyoxal (pro-apoptotic chemical). Inhibitors of PI3K, AKT, and mTOR reduced this effect with the mTOR inhibitor showing the greatest effect.[133] Therefore this mechanism and pathway needs further

investigation as a potential novel treatment strategy in TBI.

FIGURE 3- OVERVIEW OF MAIN PATHWAYS INDUCED BY GLP-1 IN NEURONS



Overview of the major pathways induced by GLP-1 in neurons. Activation of the GLP-1R activates an adenylyl cyclase and increases cAMP levels as well as PI3K. This activate other downstream kinases that are related to growth factor signalling, autophagy and apoptosis.

2. Normal Physiology of ICP in IIH

2.1. Introduction

Humans ordinarily maintain an upright posture throughout the day whilst adopting a horizontal posture for sleep. In usual clinical practice, ICP is measured in the left lateral position traditionally adopted for the lumbar puncture position which is most commonly utilised for diagnostic measurement.

Previous work has investigated postural changes in ICP in disease states with raised ICP but not specifically IIH. ICP has been shown to vary with posture both between horizontal and vertical states [27, 30, 134] and also with variations in horizontal postures including between supine and left lateral positions and with neck or hip flexion.[28] ICP has been shown to be higher during sleep in a cohort of patients with hydrocephalus.[135] ICP changes with posture over a 24-hour period have not been established in IIH.

In this study the normal physiological changes in ICP in IIH were evaluated in variable postures, diurnally and through sleep in a cohort of patients with active IIH utilising continuous telemetric ICP monitoring.

2.2. Hypothesis

I hypothesised that ICP would vary diurnally and between a supine and upright posture in patients with raised ICP secondary to IIH.

2.3. Aims

- Establish the optimal duration for ICP monitoring in IIH.
- Evaluate changes in ICP due to different patient postures.
- Determine if ICP changes diurnally.

2.4. Methods

2.4.1. Telemetric ICP Catheter

Raumedic p-Tel ICP catheters were inserted into participants utilising standard clinical practise as described in (IIH Pressure study protocol 2.11). The p-Tel sensor was inserted into the parenchyma of the right frontal lobe via burr hole, the procedure was performed under general anaesthesia by a single neurosurgeon with expertise in CSF surgery. The probe function was checked prior to insertion to ensure it was within tolerance, but zeroing is not required due to the probe design which ensured minimal measurement drift.[136] Participants were discharged prior to returning for baseline assessment as per the study protocol.

2.4.2. ICP recording and analysis

2.4.2.1. ICP changes over time

ICP was recorded continuously over 5-minute, 30-minute or 3-hour periods with participants adopting a fully supine posture at 0° to horizontal, without additional head support. The raw data recording was then analysed by dividing the 5-minute recordings into 1-minute blocks, 30-minute recordings into 5-minute blocks and 3-hour recordings into 30-minute blocks and calculating mean ICP from the waveform for each block utilising proprietary software (Raumedic Dataview version 1.2).

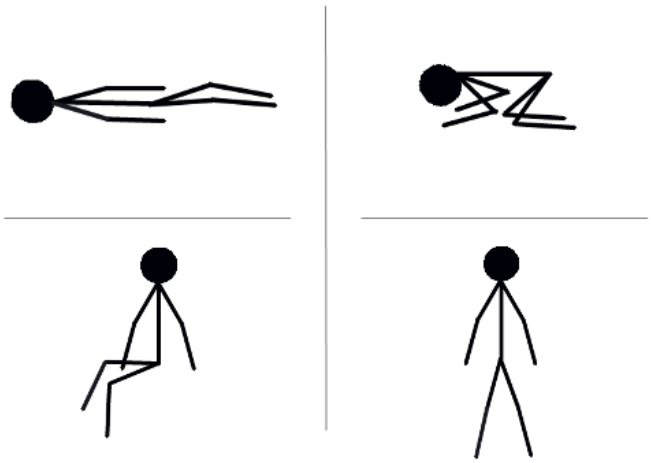
2.4.2.2. Postural changes in ICP

Evaluation of changes in ICP resulting from different postures was assessed in line with the UHB ICP monitoring protocol (Appendix k, section 8). Participants adopted supine, lumbar puncture, sitting and standing postures for 5 minutes in each position. This was followed by performing 2 bends and 2

coughs. The supine posture was fully recumbent at 0° to horizontal without additional head support. The lumbar puncture position was the left lateral position with hips flexed to 90° and knees flexed; the neck was in a neutral position with head supported to maintain neutral neck alignment. Sitting was unsupported on the edge of a hospital bed with legs dependent, standing was upright in a relaxed pose. For bending participants were instructed to flex from the hips from standing to attempt to touch the floor before returning to standing. Coughs were single maximal effort. Following each individual bend and cough participants paused for 1 minute. The postures are shown in figure 11.

The raw data recording was then analysed by calculating mean ICP from the waveform for each 5-minute period utilising proprietary software (Raumedic Dataview version 1.2).

FIGURE 4 - ILLUSTRATED POSTURES



ICP recording postures. Clockwise from top left, fully supine, head unsupported; left lateral decubitus (lumbar puncture position); standing; sitting.

2.4.2.3. Diurnal changes in ICP

Changes in ICP during the day

ICP recordings were made at pre-specified timepoints during the study baseline day whilst the participant was awake. These correspond to approximately 1100hrs, 1330hrs, 1700hrs and 2300hrs +/-1hr. Each recording was made in the supine position for 30 minutes and analysed as described above. Between recordings participants were ambulant and participating normal activities of daily living.

Changes in ICP overnight

ICP was recorded continuously overnight. Participants prepared to sleep in the clinical research facility and wore the telemetric ICP reader. They were allowed to adopt their usual posture for sleep. ICP recordings were analysed as above. The recordings were broken into 1-hour blocks from midnight. Where insufficient data were collected for a block, this was excluded.

2.4.2.4. Changes in ICP at sleep induction

ICP was recorded at the 11hr timepoint in both supine and upright postures. ICP was also subsequently recorded continuously overnight. The ICP traces were analysed to identify the point at which participants retired to sleep, the exact time of which varied by participant. 5-minute recordings were analysed in both supine and upright postures before and after the subjects retired. The ICP data was analysed as at 3.2.2.1.

2.4.3. Statistical methods

The study analysis was conducted after the final visit of the final patient. Data were analysed with GraphPad Prism 8.0 (GraphPad Software), outcomes are summarised by means with standard deviations. Values are compared using t-tests with significance set at p=<0.05.

Missing data were excluded from analysis.

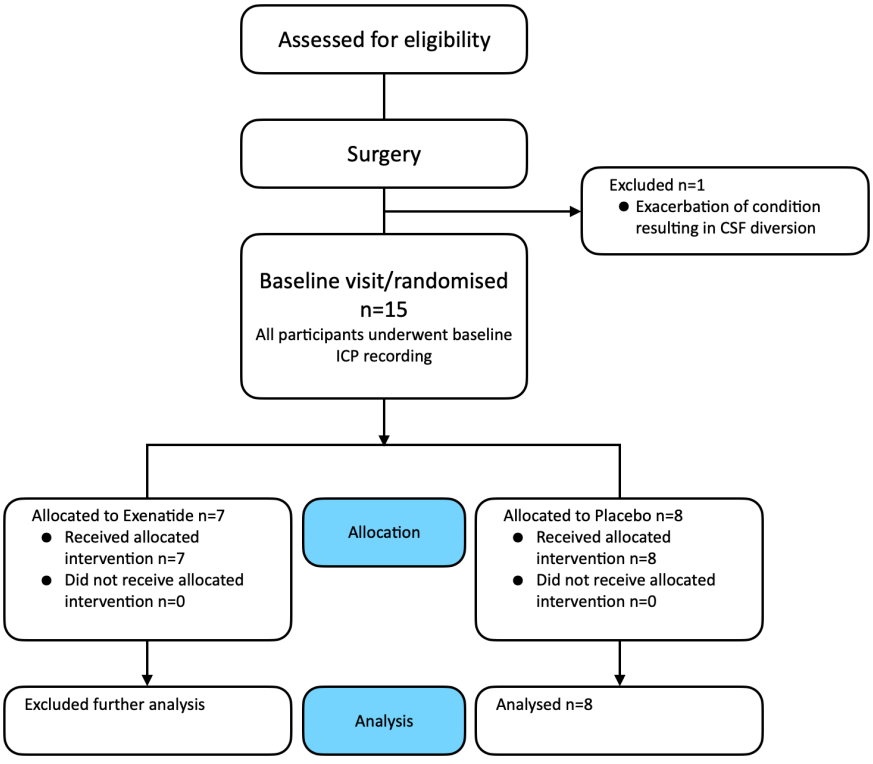
2.5. Results

2.5.1. Demographics and baseline characteristics

16 female patients were recruited to the IIH Pressure Physiology study. (Figure 5 consort) One participant was withdrawn before randomisation and in one the telemeter failed at 12-week visit and ICP data is missing at this point, although all other measures are recorded. 7 participants were randomised to the exenatide arm, these participants are excluded from physiology analysis after this timepoint.

Median (IQ range) time from surgery to baseline visit was 10 days (16.5).

FIGURE 5 - CONSORT DIAGRAM PHYSIOLOGY STUDY



Consort diagram. *Consort diagram describing the numbers and disposition of study subjects.*

TABLE 1 - BASELINE CHARACTERISTICS

	Mean (SD), n=15
Age (years) (all female)	28 (9)
BMI (kg/m^2)	38.1 (6.2)
ICP as measured with Raumedic (mmHg) supine	21.2 (4.8)
ICP converted to cmCSF (cmCSF)	28.8 (6.5)
	Median (IQR)
Frisén grade*	2 (2-3)

*BMI indicates body mass index, ICP indicates intracranial pressure, SD indicates standard deviation. * The star indicates grading the worst eye.*

2.5.2. ICP over time

Over the first 5 minutes of recording there was no significant change in ICP, table 3. Over the first 30 minutes of recording, between 0-5 and 25-30 minutes the ICP rose significantly (mean (SD)), by 3.5mmHg (2.757); p=0.0002, equivalent to a 16% increase, table 3. Subsequently ICP increased significantly over 3 hours between 0-30min and 150-180min by 2.11mmHg (2.18); p= 0.0424, equivalent to a further 9% rise. The overall rise in ICP was equivalent to 25%. (Figure 6, table 2)

TABLE 2 - ICP OVER TIME

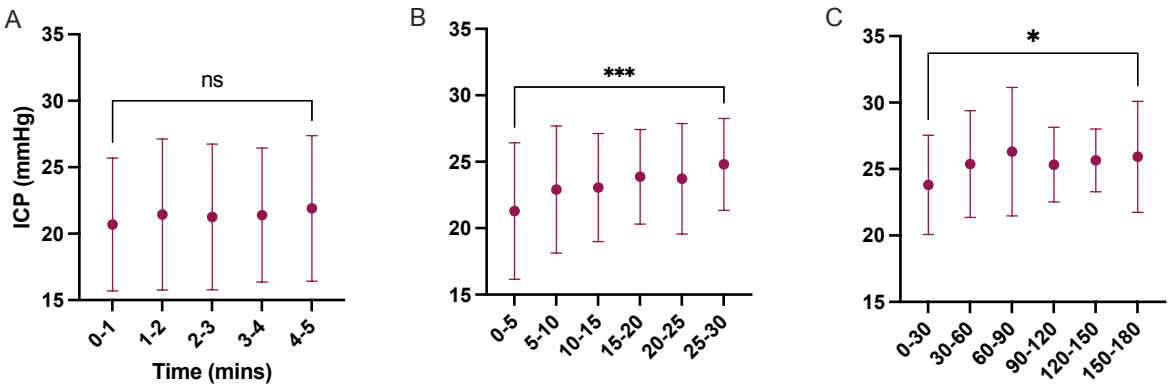
Timepoint (min)	ICP (mmHg)	Difference baseline to timepoint
	mean (SD)	**mean (SD); (95%CI), p=**
n=15		
0-1	20.7 (5.0)	

1-2	21.4 (5.9)	0.8 (2.9); (-0.8, 2.4), p=0.330
2-3	21.3 (5.5)	0.6 (3.8); (-1.5, 2.7), p=0.560
3-4	21.4 (5.0)	0.7 (3.4); (-1.2, 2.6), p=0.433
4-5	21.9 (5.5)	1.2 (3.3); (-0.6, 3.1), p=0.175
n=15		
0-5	21.3 (5.1)	
5-10	22.9 (4.8)	1.6 (1.7); (0.7, 2.5), p=0.002**
10-15	23.1 (4.1)	1.8 (2.5); (0.4, 3.1), p=0.015*
15-20	23.9 (3.6)	2.6 (2.7); (1.1, 4.1), p=0.003**
20-25	23.7 (4.2)	2.4 (3.6); (0.4, 4.4), p=0.021*
25-30	24.8 (3.5)	3.5 (2.8); (2.0, 5.0), p=0.0002***
n=7		
0-30	23.8 (3.7)	
30-60	25.4 (4.0)	1.6 (2.0); (-0.3, 3.4), p=0.080
60-90	26.3 (4.8)	2.5 (2.8); (-0.1, 5.1), p=0.056
90-120	25.3 (2.8)	1.5 (2.6); (-0.9, 3.9), p=0.174
120-150	25.7 (2.4)	1.9 (2.7); (-0.6, 4.3), p=0.116

150-180	25.9 (4.2)	2.1 (2.2); (0.1, 4.1), p=0.042*

*ICP indicates intracranial pressure, SD indicates standard deviation, CI indicates confidence, intervals, * indicates p=<0.05, ** indicates p=<0.01, *** indicates p=<0.001.*

FIGURE 6 - ICP CHANGES OVER TIME



ICP changes over time. *ICP was recorded over differential periods in the supine position. A) over 5 minutes, B) over 30 minutes, C) over 3 hours (mmHg). n = 15 (A-B) and n=7 (C). Paired t test. Data presented as mean ±SD. *P=<0.05.*

2.5.3. ICP position changes

Posture had a pronounced effect on ICP, in the supine position mean (SD) ICP was 21.2 (4.8) mmHg, in the left lateral position 24.0 (3.8) mmHg, sitting 10.1 (5.1) mmHg and standing 10.3 (3.7) mmHg. In comparing the changes from sitting to left lateral (LP) position, ICP rose 2.8 (4.0) mmHg, 13%, p=0.028; from supine to standing ICP fell 10.9 (4.2) mmHg, -51%, p=0.0001. There was no significant change between sitting and standing, 0.2 (3.8) mmHg, 2%, p=0.82. (Table 3, 4, Figure 7)

TABLE 3 - POSTURAL ICP

Position	ICP mean (mmHg) (SD)
Supine	21.2 (4.8)
Left lateral (LP)	24.0 (3.8)
Sitting	10.1 (5.1)
Standing	10.3 (3.7)

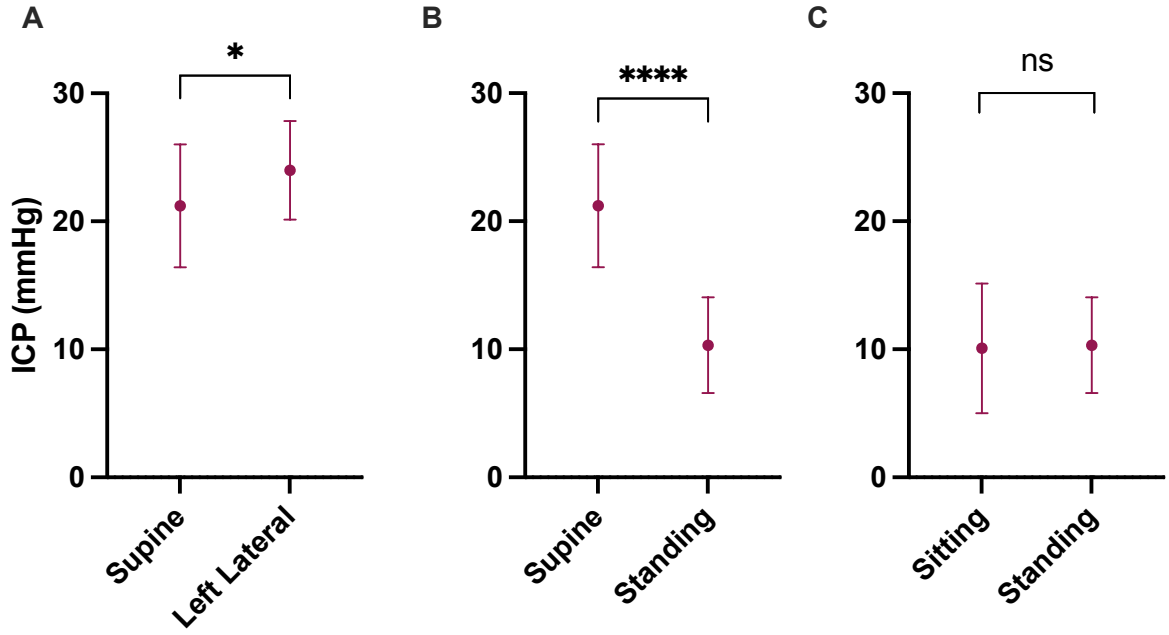
ICP indicates intracranial pressure, SD indicates standard deviation.

TABLE 4 - POSITION CHANGE ICP

Position change	ICP change mean (mmHg) (SD)	mean % change	p Value
Supine to LP	2.8 (4.0)	13%	0.028*
Supine to standing	-10.9 (4.2)	-51%	0.0001****
Sitting to standing	0.2 (3.8)	2%	0.82

*ICP indicates intracranial pressure, SD indicates standard deviation, LP indicates lateral decubitus position, * indicates p=<0.05, **** indicates p=<0.0001.*

FIGURE 7 - ICP CHANGES WITH POSTURE



ICP changes with posture. *ICP was recorded in the supine, left lateral, sitting and standing postures. Graphs show ICP in mmHg against A) supine and left lateral, B) supine and standing C) sitting and standing. n = 15 (A-C). Paired t test. Data presented as mean ±SD. *P=<0.05*

2.5.4. ICP diurnal variability

2.5.4.1. Daytime diurnal variability

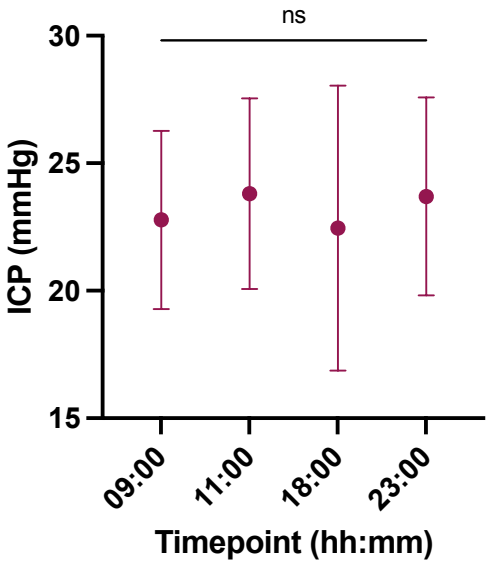
There was no significant change between timepoints during waking hours. (Figure 8, table 5)

TABLE 5 - DIURNAL CHANGE DAY

Timepoint (hh:mm) n=7	ICP mean (mmHg) (SD)	Difference baseline to timepoint mean (SD); (95%CI), p=
09:00	22.8 (3.5)	-
11:00	23.8 (3.7)	1.0 (2.2); (-1.0, 3.0), p=0.259
18:00	22.5 (5.6)	-0.3 (3.2); (-3.3, 2.7), p=0.801
23:00	23.7 (3.9)	0.9 (1.5); (-0.5, 2.3), p=0.155

ICP indicates intracranial pressure, SD indicates standard deviation, CI indicates confidence intervals.

FIGURE 8 - ICP DOES NOT SHOW DIURNAL VARIABILITY



ICP does not show diurnal variability. *ICP was recorded at timepoints throughout waking hours. Graph shows ICP in mmHg at 0900, 1100, 1800 and 2300. n = 7. Paired t test. Data presented as mean ±SD. *P=<0.05.*

2.5.4.2. Night-time diurnal variability

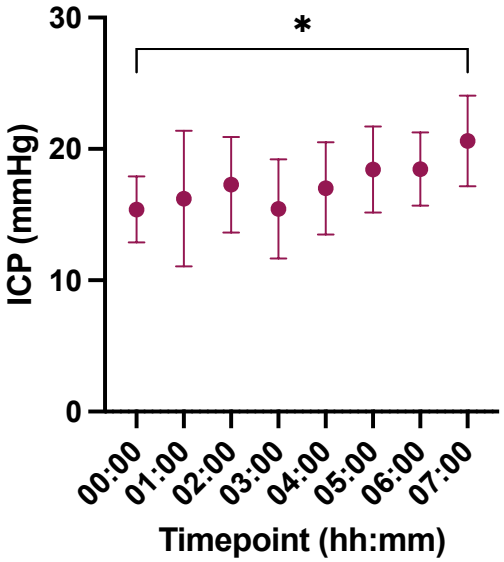
ICP increased overnight, there was a significant difference between ICP at 0700 compared to midnight of 4.02 mmHg (1.772), p=0.02, equivalent to a 34% rise. (Figure 9, table 6)

TABLE 6 - DIURNAL CHANGE NIGHT

Timepoint (hh:mm) n=6	ICP mean (mmHg) (SD)	Difference baseline to timepoint mean (SD); (95%CI), p=
Midnight	15.4 (2.5)	-
01:00	16.2 (5.2)	0.0 (5.1); (-6.3, 6.3), p=0.989
02:00	17.3 (3.6)	0.7 (3.7); (-3.9, 5.3), p=0.695
03:00	15.4 (3.8)	0.5 (4.6); (-5.2, 6.2), p=0.815
04:00	17.0 (3.5)	1.5 (3.6); (-3.0, 5.9), p=0.411
05:00	18.4 (3.3)	2.7 (5.3); (-3.9, 9.3), p=0.319
06:00	18.5 (2.8)	3.1 (3.1); (-0.8, 7.0), p=0.090
07:00	20.6 (3.4)	4.0 (1.8); (1.2, 6.8), p=0.020*

*ICP indicates intracranial pressure, SD indicates standard deviation, CI indicates confidence, intervals, * indicates p=<0.05.*

FIGURE 9 - ICP INCREASES OVERNIGHT



ICP increases overnight. *ICP was recorded overnight whilst supine. Graph shows ICP in mmHg averaged hourly between midnight and 07:00. n = 6. Paired t test. Data presented as mean ±SD. *P=<0.05.*

2.5.4.3. Sleep induction

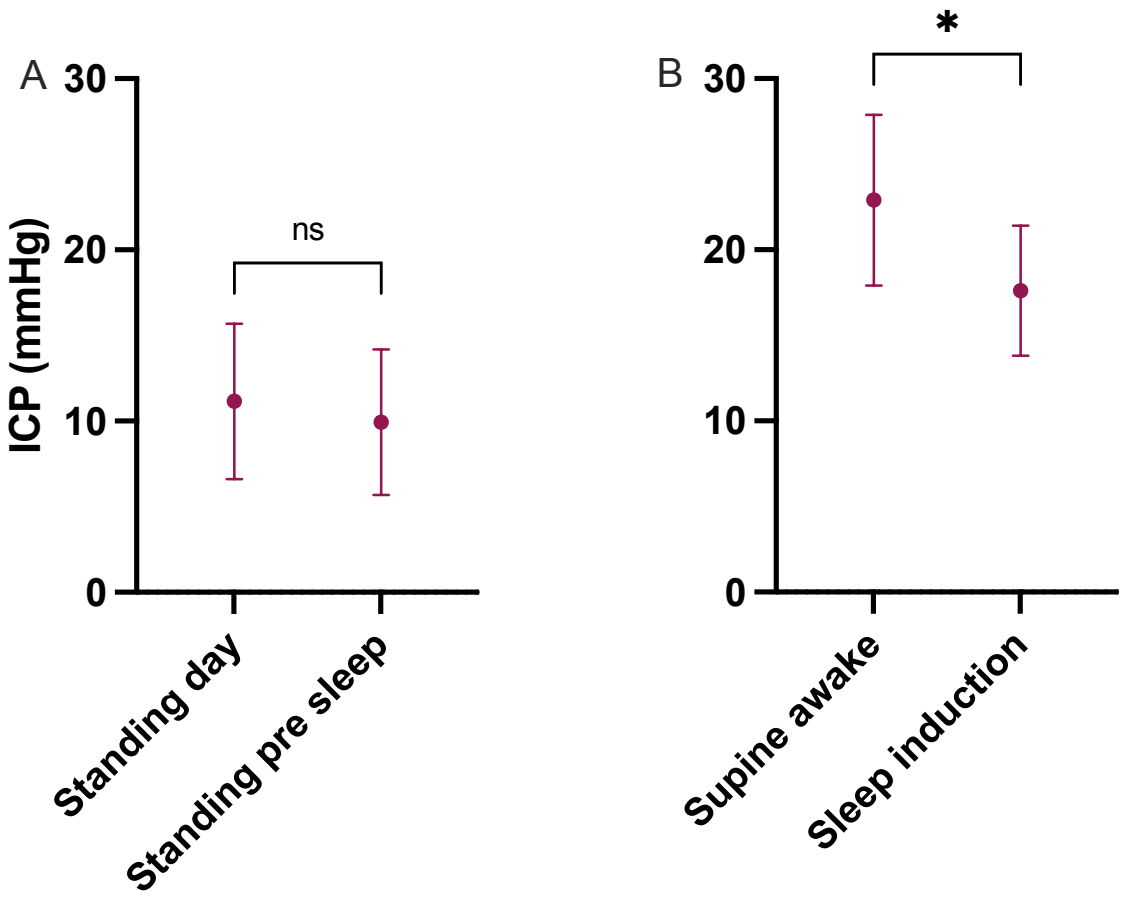
I demonstrated that during the day intermittent ICP recording is stable (table 5, 2.5.4.1) and standing ICP recording is also stable. I note that ICP after adopting a supine posture for a 5-minute interval prior to sleep was significantly lower than during waking hours, -5.3mmHg (3.8), p=0.0194, equivalent to 23% fall. (Figure 10, table 7)

TABLE 7 - SLEEP INDUCTION

ICP recording n=6	ICP mean (mmHg) (SD)	Difference baseline to timepoint mean (SD); (95%CI), p=
Supine awake	22.9 (5.0)	-5.3 (3.8); (-9.3, -1.3), p=0.019*
Supine sleep induction	17.6 (3.8)	
Standing day	11.2 (4.5)	-1.2 (2.3); (-3.6, 1.1), p=0.242
Standing pre sleep induction	9.9 (4.3)	

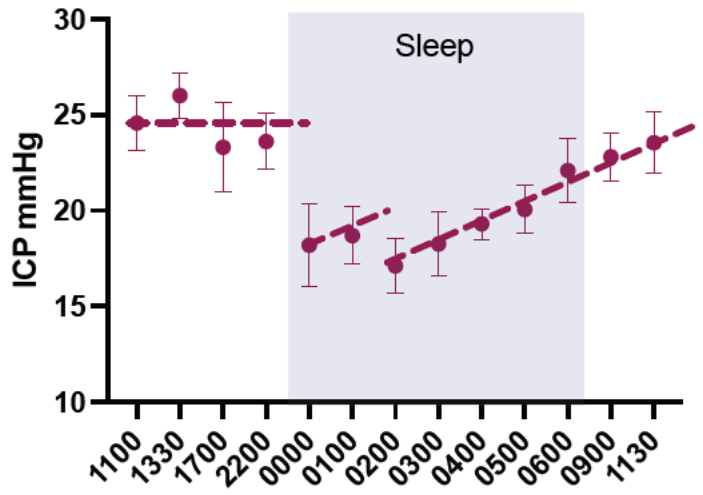
*ICP indicates intracranial pressure, SD indicates standard deviation, CI indicates confidence, intervals, * indicates p=<0.05*

FIGURE 10 - ICP FALLS AT SLEEP INDUCTION



ICP falls at sleep induction. *ICP was recorded before and after retiring to sleep. Graphs show ICP in mmHg A) standing during day vs pre sleep and B) supine whilst awake vs at sleep induction. n = 6. Paired t test. Data presented as mean ±SD. *P=<0.05.*

FIGURE 11 - INFOGRAM SLEEP ICP CHANGE



***ICP changes in sleep**. Infogram demonstrating ICP changes, no diurnal variability during daytime supine recording. ICP lower at beginning of sleep but then increases over the course of the night.*

2.6. Discussion

No previous studies have investigated the physiological characteristics of ICP in a cohort of patients with IIH. This study has demonstrated three key findings in IIH, that ICP rises with time in the supine position, that ICP rises during overnight and that there is no diurnal variability of ICP during waking hours.

Establishment of raised ICP is a key clinical criterion of the diagnosis of IIH, in clinical practise this is usually achieved by lumbar puncture, though increasing use is being made of more invasive ICP measurement in some circumstances. Lumbar puncture can be challenging in this cohort owing to body habitus and provides limited information. Only a single ICP measurement is recorded by visual inspection of a manometer during the procedure. ICP is by necessity recorded in the left lateral position, although previous work has attempted to relate pressure recorded in this position to those sitting without success.[24] Currently sitting ICP is not used in clinical practice.

Previous work has established an ICP cut-off at 25cmCSF for diagnosis of IIH, [25] which is used in current guidelines[1, 13] though there remains uncertainty regarding the validity of the cut-off measured at a single timepoint, as the natural history of ICP in IIH is unknown.[26]

This study is the first to analyse ICP in detail over time, following the adoption of different positions in IIH. The postural variability of ICP in IIH is discussed below. Determining change in ICP after adopting a posture is critical, as a defined protocol for measuring ICP has not yet been widely established in clinical practice. In previous work detailing the effects of posture changes in a cohort of patients with raised intracranial pressure due to heterogenous pathologies, *Andresen et al.* utilised

median pressure over a 10-minute interval following each posture change after an unspecified time period to allow the ICP to stabilise. [27] In this study we have shown that in an IIH cohort, ICP rises with time following adoption of the supine posture. Although not significant statistically this effect can be observed within the first 5-minutes and continues to be seen over both 30-minute and 3-hour time horizons.

These findings have significant implications for standardising the approach to clinical measurement of ICP. The study cannot address whether this is an attribute solely of IIH physiology or if it would be present in other conditions or normality.

This study is also the first to investigate the effect of postural changes on ICP in IIH. I have confirmed previous findings, in studies of cohorts with heterogenous disease of raised ICP, that ICP rises with the adoption of the left lateral position and that ICP falls in both the sitting and standing positions. I have expanded this knowledge to IIH and shown that ICP falls 50% changing from supine to standing and increases 13% changing from supine to the lumbar puncture position. Further I have shown that there is no significant statistical difference between the sitting and standing positions. This has implications for clinical monitoring in that measurement of both sitting and standing positions is un-necessary.

Andresen et al. previously observed that ICP measurement in the left lateral position presents a distorted view of the ICP state of a patient being elevated above the supine posture, a finding confirmed in the IIH cohort by this study.[27] Detailed work by *Pedersen et al.* has gone on to show that the measurement of ICP in the left lateral position is fraught, with small changes in posture of

the neck and hips having marked effects on the recorded ICP.[28] Although guidelines state that ICP should be measured with hips flexed to 90° [13] the frequent difficulty of performing the procedure in this cohort, given the phenotype of abdominal adiposity which can limit hip flexion, highlights the need to reconsider the optimal position for standardised ICP measurement in IIH.

The lumbar puncture will remain the mainstay of ICP measurement for most patients, and its drawbacks are already recognised in current guidelines.[1] The increasing utility of invasive ICP measurement demonstrates a need for parallel diagnostic ICP criteria based on representative postures, most likely supine. The challenge of attaining normative ICP measures will remain, owing to the ethical problems in subjecting healthy volunteers and patients to more invasive procedures. However, efforts have recently been made utilising pseudo-normal populations. *Andresen et al.* reported ICP in 4 patients following removal of well demarcated brain tumours [29] and *Petersen et al.* reported ICP readings in 9 "*as normal as possible*" patients who following investigation were found to have no neurosurgical problem.[30] Most recently *Norager et al.* have reported a systematic review aiming to establish normative cut-offs for both lumbar CSF pressure and supine ICP. [31]

A widely held belief in international literature is that ICP varies diurnally.[1] This may relate to differences observed between sleep and daytime recording which are naturally in different postures, and between supine and erect postures respectively. This study has shown that there is no daytime variability in ICP in this cohort of patients with active IIH.

There are previous studies of ICP during sleep. *Ogashiwa et al*. reported a series of patients undergoing monitoring post-operatively for a variety of indications including normal pressure hydrocephalus.[32] *Riedel et al*. reports the observation of B-waves in patients undergoing monitoring and sleep studies following aneurysm closure with the finding of B-waves associated with sleep-related breathing disturbance.[33] *Chari et al.* present a large series in patients with hydrodynamic disturbances stratified into day and night recordings[34] and *Langvatn et al.* investigated a series of children with cranial syntosis.[35] The only study reporting analysis of ICP over sleep was *Ogashiwa et al.* in a single case of a patient with Chiari malformation where pressure was observed to rise until a newly inserted shunt valve opened dropping pressure.[32] The interpretation of the above studies is limited by the limitations in the number of patients, length and nature of recording and heterogeneity of the diseases and circumstances of the studies.

This study demonstrates rising pressure over the course of a night in a cohort of patients with active IIH. Detailed analysis of the transition to adopting a sleep position demonstrates no change in ICP prior to retiring to sleep in either supine or vertical positions, however the pressure immediately on lying down at sleep induction was lower than daytime recorded supine ICP. This is a novel and unexpected observation. The underlying mechanism has not been explored in this study but would be of future interest.

The observation that ICP rises overnight is important. Early morning headache is a classical feature of IIH and may be indicative of the higher ICP following sleep, anecdotally many IIH patients report sleeping sat up to mitigate early morning headache. Furthermore, in patients following a normal day-night routine the night-time period in a recumbent position represents the longest period of exposure to highest ICP, thus nocturnal elevated and rising ICP may play a significant role in the

disease pathology. This could also provide opportunity for intervention with tailoring treatment to preferentially reduce nocturnal ICP.

The study has a number of limitations. The findings of this study are only applicable to IIH. Extrapolation of the results to other diseases and normal physiology cannot be assumed. Normative ICP data for comparison are lacking. This has been a challenge for all previous studies and will remain so owing to the ethical objection to invasive recording in normal volunteers. A further limitation of this study is the small sample size owing, in particular over longer recording periods. This is due to its derivation from the IIH pressure study where sample size was governed by the power required for that study. In addition to these, challenges in recording did result in further missing data for some aspects of the physiology study reported. Missing data, for example due to interruption of recording, was excluded from analysis.

The analysis of prolonged recordings is also hampered by lack of corresponding data on real-time posture, this could be addressed in future with wearable accelerometers, similarly the overnight recordings in this study were not accompanied by EEG recording limiting conclusions that could be drawn relating to sleep state.

This study has made important findings on the way to utilising detailed ICP analysis in future clinical practice. Future extensions of this study should focus on further detailed analysis of ICP waveforms and linking that analysis to clinical characteristics. More work is required to identify the optimal time horizon for measuring ICP diagnostically in IIH. The observation of rising ICP with time in a supine

posture also gives rise to whether that rise itself has diagnostic or prognostic information and addressing that question would be of value.

One of the most pressing problems to be solved for analysing invasive ICP in patients with IIH is establishing the optimal posture, time and duration of ICP recording for diagnosis. This study would suggest time of day is not important, my findings indicate that the supine posture should be measured over a 5-minute duration and patients should not be supine for variable periods pre-recording. This is due to ICP being stable for only the first few minutes after adopting that posture.

This is also translatable to the lumbar puncture, patients usually adopt the position for a variable period whilst the procedure is accomplished, an alternative is that the lumbar puncture is completed in the sitting position with patients then adopting the traditional lumbar puncture position for the measurement of ICP immediately after the needle is sited.

2.7. Conclusion

This study is the first to undertake detailed ICP analysis in a cohort of patients with acute IIH. It has reported novel findings of increasing ICP in supine postures with time, demonstrated a lack of daytime diurnal variability in ICP and demonstrated increasing ICP during overnight recording. These findings have important implications for the recording and interpretation of invasive ICP monitoring in IIH patients which is increasing in use clinically and also provides insights into aspects of IIH pathophysiology.

3. IIH Pressure Main Trial

3.1. Introduction

Idiopathic Intracranial Hypertension (IIH) is characterized by increased intracranial pressure (ICP) with no identifiable cause. Recent weight gain is the major risk factor for development of the condition and its occurrence is most commonly observed in overweight women of reproductive age. [3, 11] The incidence of IIH is rising[137] and the incidence appears related to the prevalence of obesity.[4] Chronic disabling headaches occurs in the majority and there is a risk of blindness.[11] [138] Currently there is no licenced therapy for IIH: this is a clear unmet clinical need for patients, which was highlighted by a priority setting partnership.[12]

Glucagon-like peptide 1 (GLP-1) is a gut neuropeptide secreted by the distal small intestine in response to a meal[139]. GLP-1 agonists are used to reduce blood sugar in the treatment of diabetes, as GLP-1 stimulates glucose dependant insulin secretion and inhibits glucagon release, thereby lowering blood glucose but not causing hypoglycaemia. [85] GLP-1 is also synthesised in neurons of the nucleus tractus solaris that project to the hypothalamus and this is the mechanism by which it is known to help regulate satiety and weight loss.[90] GLP-1 agonists have been licenced for weight loss in the setting of obesity.[140]

GLP-1 has a role in fluid secretion, it has been shown to reduce sodium reabsorption and promotes diuresis through action in the renal proximal tubule[92, 93] Preliminary data from the Sinclair group has shown that GLP-1R is expressed in the choroid plexus, that stimulation reduces CSF secretion and that GLP-1 reduces ICP in an *in vivo* model.[96]

The aim of this study is to evaluate the biological effect of acute and chronic administration of a GLP-1 agonist, Exenatide, on ICP in a cohort of patients with IIH, utilising telemetric ICP monitoring.

3.2. Hypothesis

- I hypothesised that a single administration of exenatide would reduce intracranial pressure (ICP).

- I hypothesised that repeated administration of exenatide would reduce intracranial pressure (ICP).

- I hypothesised that repeated administration of exenatide causing a lowering of ICP would make an impact on IIH by reducing headache severity and frequency, and should therefore improve the quality of life.

3.3. Aims

3.3.1. Primary Aims

- The aim of this randomised clinical trial (RCT) was to assess the biological action of a single administration of Exenatide on ICP.
- The trial would also assess the biological action of repeated administration of Exenatide on ICP.

3.3.2. Secondary Aims

- The secondary aims of the trial were to evaluate the clinical impact of lowering ICP by repeated dosing of exenatide and what impact this would have on headache severity and frequency, and quality of life in people with active IIH.

3.4. Methods

The IIH pressure study protocol is at section 8.

3.4.1. Telemetric ICP Catheter

Raumedic p-Tel ICP catheters were inserted into participants utilising standard clinical practise as described in section 8.11.

3.4.2. ICP recording and analysis

ICP was recorded continuously, at specified timepoints participants adopted a fully supine posture at 0° without additional head support. The raw data recording was then analysed by calculating mean ICP from the waveform for each block utilising proprietary software (Raumedic Dataview version 1.2).

3.4.2.1. Primary outcomes

At baseline and each timepoint (2.5 hours post drug administration at day 0, day 1 and week 12) ICP was recorded for 30 minutes in the supine position.

3.4.2.2. Exploratory

2.5-hour time course

ICP was recorded continuously over 30 minutes at baseline and 2.5 hours post drug administration with participants adopting the above supine posture. The raw data recording was then analysed by calculating mean ICP from the waveform for each block utilising proprietary software (Raumedic Dataview version 1.2), the data following drug administrations was divided into discrete 30-minute blocks for analysis.

3.4.2.3. Overnight time course

ICP was recorded continuously overnight. Participants prepared to sleep in the clinical research facility and wore the telemetric ICP reader. They were allowed to adopt their usual posture for sleep. ICP recordings were analysed as above. The recordings were broken into 1-hour blocks from midnight. Where insufficient data were collected for a block, this was excluded.

3.4.3. Body mass index

BMI was measured from height and weight using the formula: BMI= (weight(kg))/(height (m))^2. Height was recorded standing without shoes or hats (Seca Leicester height measure, Birmingham, UK) and weight was recorded following removal of shoes and outdoor clothing (Tanita, Netherlands).

3.4.4. Visual assessments

Visual assessments were performed at baseline, 6 hours, 24hours, week 2 and week 12. Vision was corrected with glasses, contact lenses, optical lenses, or pinhole as appropriate.

3.4.5. Visual acuity

Visual acuity was recorded with best corrected vision utilising logMAR (logarithm of the minimum angle of resolution) measured using ETDRS charts (Precision Vision, USA), following normal clinical practice.

3.4.6. Automated visual field perimetry

Visual field perimetry was performed with a Humphrey field analyser (Carl Zeiss Meditec, Dublin, USA) utilising the Swedish Interactive Threshold Algorithm (SITA) standard 24-2 central threshold programme.

3.4.7. Ocular coherence tomography

Ocular coherence tomography (OCT) was performed using spectral domain optical coherence tomography with the Heidelberg Spectralis SD-OCT (Heidelberg Engineering, Franklin, USA). Each eye was analysed with an automated peripapillary Retinal Nerve Fibre Layer (RNFL) scan using 100 automatic real-time (ART) records. The average global peripapillary RNFL was recorded.

3.4.8. Intraocular pressure

Intraocular pressure (IOP) was measured in the supine position, without anaesthesia, using an iCare IC200 tonometer (iCare, Raleigh, USA).

3.4.9. Assessment of papilloedema by Frisén grade

A neuro-ophthalmologist graded papilloedema using the Frisén classification,[141] here 0 denotes no papilloedema to grade 5 being the most severe papilloedema as part of the eligibility criteria for study inclusion.

3.4.10. Headache

At baseline a detailed clinical, medication and headache history was taken (including the location, character, associated symptoms, timing and exacerbating/relieving factors. The headache phenotype was then recorded using the International Classification of Headache Disorders (ICHD-3 beta) criteria for primary and secondary headache disorders.[142]

Daily headache diaries (Appendix g, section 8) were completed for 1 month prior to surgery (for placement of the telemetric ICP monitor) and prior to week 12. The diaries included details of headache severity; headache duration; headache frequency (monthly headache days); and analgesic use (days per month). The headache severity was scored using a numerical rating scale ranging from 0 (no pain) to 10 (the most severe pain level experienced by the subject).

3.4.11. Quality of life

Quality of Life outcome measures included the headache impact test-6 disability questionnaire (HIT-6); where little or no impact = HIT-6 score ≤49; some impact = HIT-6 score 50–55; substantial impact = HIT-6 score 56–59; severe impact = HIT-6 score ≥ 60. Health-related quality of life was assessed using the Rand patient-reported 36-Item Short Form Health Survey (SF-36). The eight sections of the SF-36 yielded two summary scores (physical component summary, PCS; and mental component summary, MCS). (Appendix J, section 9) These were completed by participants at baseline and week 12.

3.4.12. Safety

Patients attended the trial visits fasted. Blood was drawn via a cannula in a peripheral vein following usual clinical procedure. Blood was tested in the University Hospitals Birmingham NHS Foundation Trust clinical laboratory for renal function (creatinine), liver function (ALT), lipid profile (total cholesterol and triglycerides) and HbA1C to assess drug safety.

3.4.13. Adverse event reporting

See section 8.12.

3.4.14. Statistical considerations

See also section 8.16.

3.4.14.1. Randomisation

Eligible participants were randomized by a paper randomisation system administered by the Birmingham Clinical Trials Unit. Allocation was 1:1 (Exenatide: placebo).

3.4.14.2. Sample size

The study proposes to investigate the effect of GLP-1R agonist on the continuous variable, intracranial pressure (ICP) via a two-arm, randomised, study. The primary outcome will be change in ICP.

In a study of 25 patients, Sinclair et al[56] showed that the cross-sectional sample standard deviation of ICP is 4.9 – 5.1 cm H_2O, measured at baseline and immediately before and after a longitudinal

intervention (low energy diet). It is felt that a reduction in ICP of 5 cm H_2O would be clinically meaningful.

Seeking significance at least 5% and power at least 90% using equal group sizes, a total sample size of 14 patients are required, i.e. 7 patients will be randomised to receive active treatment and a further 7 to receive control. This calculation assumes that the standard deviation of ICP is 5.1, the upper end of the range observed previously. [Allowing for 10% drop-put, the proposed recruitment is 8 patients per arm, and 16 patients in total]

3.4.14.3. Planned analysis

All primary analyses (primary and secondary outcomes including safety outcomes) were evaluated by intention-to-treat (ITT) analysis. Analysis was completed on received data, with every effort made to follow-up participants to minimize potential for bias. Final analyses were conducted after the final visit of the final patient of the main trial once the data had been cleaned and locked; then unblinded. No imputation of missing data was conducted. The analysis of visual data included data from the most affected eye at baseline as defined by PMD, analysis of intra-ocular pressure was performed on the mean average of both eyes. Statistical analysis was performed in R v4.0.0 (R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism 8.0 (GraphPad Software). Data were reported as means and SD (with median and interquartile range [IQR] for non-normal data), and SE and 95% confidence intervals (CI) where appropriate. Hierarchical linear regression models were used to analyse repeated measures of the primary and secondary outcomes and to estimate differences adjusted for baseline values. In these models, population-level effects (also known as fixed effects) comprised the intercept, time as a factor variable, and the 2-way interaction of treatment arm and time as a factor variable to model changing treatment effects over time. Group-level effects (also known as random effects) comprised patient-level adjustments to the

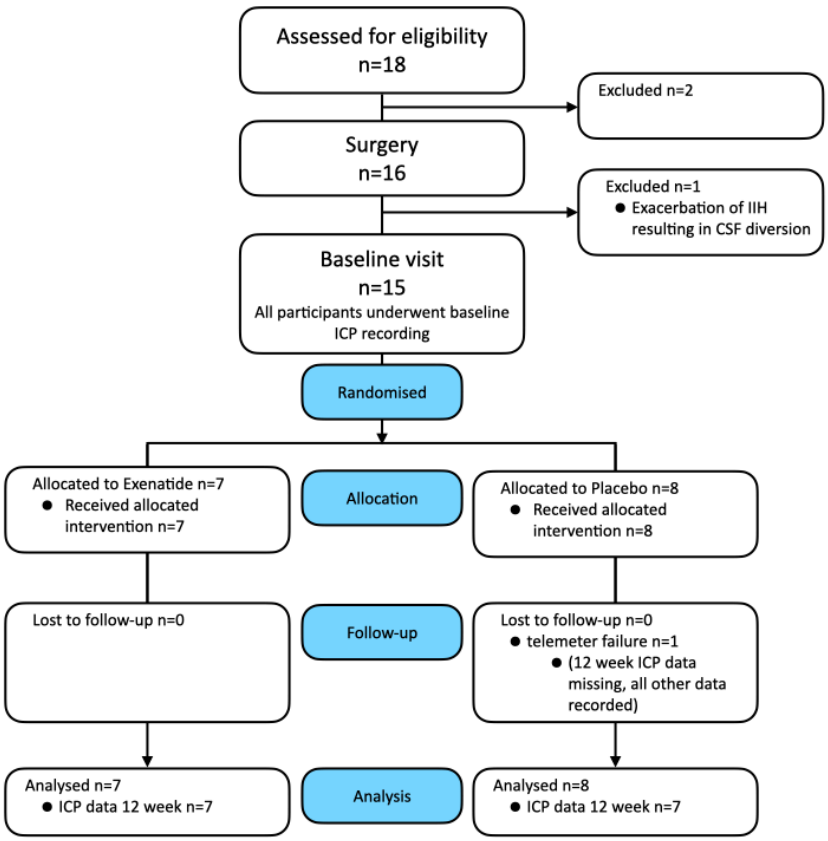
intercept. The hierarchical regression model addresses the multiple comparisons problem using semi-Bayes adjustment. The threshold for statistical significance was pre-specified at 0.1.

3.5. Results

3.5.1. Baseline characteristics

16 female patients were recruited to the IIH Pressure study, (Figure 12 consort). One participant was withdrawn before randomisation, due to exacerbation of their condition necessitating escalation of their management. In one participant the telemeter failed at the 12-week visit and hence ICP data is missing at this point, although all other measures were included. 7 participants were randomised to the exenatide arm, and 8 to the placebo arm.

FIGURE 12 - CONSORT DIAGRAM



Consort diagram. *Consort diagram describing the numbers and disposition of study subjects.*

Age, BMI and ICP at baseline were well matched between groups. At baseline there was a significant difference in monthly headache days between arms (table 9), exenatide 21.6 (5.2) (mean (SD)) and placebo 10.3 (8.5), p=0.009; there was also a significant difference in perimetric mean deviation, exenatide -0.6 (1.0) (mean(SD)dB) and placebo -2.7 (1.9), p=0.025. Median (IQ range) time from surgery to baseline visit was 10 days (16.5). (Table 8)

TABLE 8 - BASELINE CHARACTERISTICS

	All	**Exenatide**	**Placebo**
	Mean (SD)	Mean (SD)	Mean (SD)
Number	15	7	8
Duration of IIH at enrolment (years)	51 (97)	31 (61)	69 (121)
Age (years)	28 (9)	28 (13)	28 (6)
BMI (kg/m^2)	38.1 (6.2)	37.6 (7.9)	38.6 (4.7)
ICP (supine) mmHg	23.5 (3.9)	22.3 (3.6)	24.6 (4.1)
ICP (LP position) cm CSF	32.2 (5.6)	30.7 (6.7)	33.5 (5.6)
Frisen Grade (Worst eye)*	2 (2-3)	2 (2-2)	2.5 (2-3)

Baseline characteristics. IIH, idiopathic intracranial hypertension; BMI, body mass index; ICP, intracranial pressure; LP, lumbar puncture.

3.5.2. Primary outcome measures

Following drug administration there was an acute and significant fall in ICP (Table 9 and figure 13). At 2.5 hours ICP fell by 4.2 (1.9) (mean (SD) mmHg), p=0.031, and at 24 hours by 4.7 (2.1), p=0.030. The effect was sustained at 12 weeks with an ICP reduction of 4.6 (2.5), p=0.058.

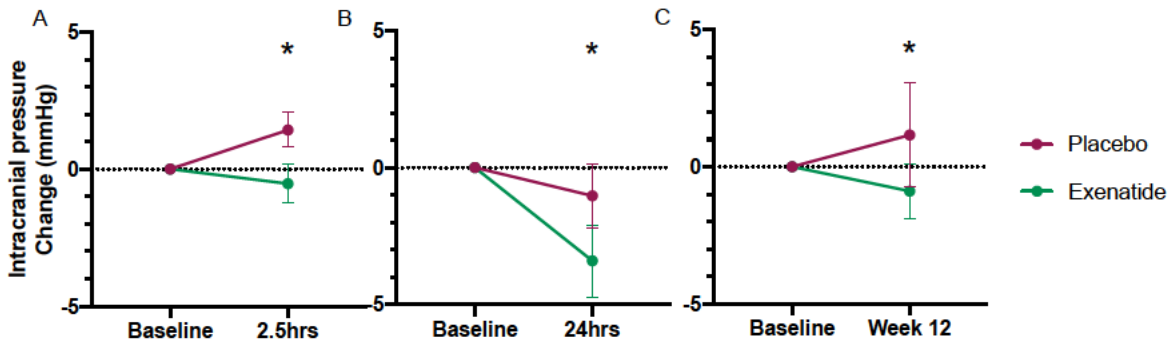
TABLE 9 - PRIMARY OUTCOME MEASURES

	Baseline	**Time point**	**Difference baseline to time point**	**Difference between arms at time point**	
				t-test	Hierarchical regression
	mean (SD)		mean (SD); 95%CI, p	mean (SE); 95%CI, p	mean (SE); 95%CI, p
ICP 2.5 hours (mmHg)					
Exenatide	22.3 (3.6)	21.8 (3.4)	-0.5 (1.9); (-2.3, 1.2), p=0.485	-4.2 (1.9); (-8.0, -0.4), p=0.031	-4.2 (2.1); (-8.4, 0.0), p=0.048*
Placebo	24.6 (4.1)	26.0 (3.4)	1.4 (1.8); (-0.1, 2.9), p=0.060		
ICP 24 hours (mmHg)					
Exenatide	22.3 (3.6)	18.9 (5.3)	-3.4 (3.5); (-6.6, -0.2), p=0.042	-4.7 (2.9); (-10.3, 0.9), p=0.095	-4.7 (2.1); (-8.8, -0.5), p=0.030*

Placebo	24.6 (4.1)	23.5 (4.5)	-1.0 (3.3); (-3.8, 1.7), p=0.406		
ICP 12 weeks (mmHg)					
Exenatide	22.3 (3.6)	21.4 (4.0)	-0.9 (2.7); (-3.3, 1.6), p=0.410		
Placebo	24.6 (4.1)	26.0 (4.4)	1.2 (5.1); (-3.5, 5.8), p=0.565	-4.6 (2.5); (-9.5, 0.3), p=0.064	-4.1 (2.2); (-8.4, 0.1), p=0.058*

Primary outcome measures. ICP, intracranial pressure. * Indicates p=≤0.1.

FIGURE 13- PRIMARY OUTCOME MEASURES



***ICP reduces with single and repeated exenatide administration**. ICP was recorded over 30 minutes, supine at baseline and after drug dosing. Graphs show change in ICP between baseline and A)2.5hours, B) 24 hours, C) at week 12.*

3.5.3. Exploratory ICP

3.5.3.1. Overnight ICP

Overnight ICP recording showed a lower ICP in the exenatide arm. ICP was 4.9(2.5) mmHg (mean (SD)) (6.6cmCSF) lower at 0600hrs, p=0.048. (Table 10, Figure 14)

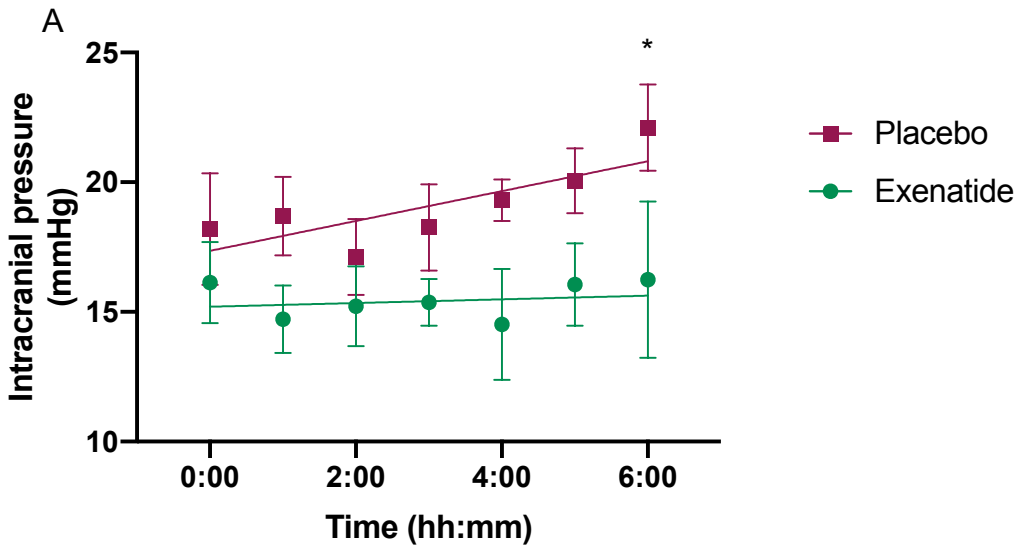
TABLE 10 - OVERNIGHT ICP

Time (24 hours)	Baseline	At time point	Difference baseline to time point	Difference between arms at time point	
				t-test	Hierarchical regression
	ICP (mmHg) mean (SD)		mean (SD); 95%CI, p	mean (SE); 95%CI, p	mean (SE); 95%CI, p
Midnight					
Exenatide	16.1 (3.5)	16.1 (3.5)	-	-2.1 (3.0); (-8.0, 3.9), p=0.455	-2.5 (2.3); (-7.1, 2.1), p=0.284
Placebo	18.2 (5.7)	18.2 (5.7)	-		
01:00					
Exenatide	16.1 (3.5)	14.7 (3.2)	-0.7 (2.1); (-3.3, 1.9),	-4.0 (2.2); (-8.4, 0.4), p=0.072	-4.0 (2.3); (-8.4, 0.5), p=0.082
Placebo	18.2 (5.7)	18.7 (4.0)	0.5 (4.1); (-3.3, 4.3),		
ICP 02:00 (mmHg)					
Exenatide	16.1 (3.5)	15.2 (3.8)	-0.6 (3.1); (-4.5, 3.2),	-1.9 (2.4); (-6.6, 2.8), p=0.392	-1.9 (2.3); (-6.4, 2.6), p=0.406
Placebo	18.2 (5.7)	17.1 (3.9)	-1.1 (4.1); (-4.9, 2.7),		
ICP 03:00 (mmHg)					
Exenatide	16.1 (3.5)	15.4 (2.2)	-0.5 (1.7); (-2.6, 1.6),	-2.9 (2.2); (-7.1, 1.4), p=0.161	-2.9 (2.3); (-7.4, 1.6), p=0.206
Placebo	18.2 (5.7)	18.3 (4.4)	0.1 (2.7); (-2.4, 2.5),		
ICP 04:00 (mmHg)					
Exenatide	16.1 (3.5)	14.5 (4.8)	-0.2 (2.5); (-4.2, 3.8),	-6.2 (3.1); (-12.3, -0.1), p=0.047	-5.6 (2.3); (-10.1, -1.0), p=0.018
Placebo	18.2 (5.7)	20.7 (4.1)	2.5 (5.1); (-2.2, 7.3),		

ICP 05:00 (mmHg)					
Exenatide	16.1 (3.5)	16.1 (3.2)	0.5 (2.7); (-3.8, 4.7),	-4.0 (2.5); (-8.9, 0.9),	-4.2 (2.5); (-9.1, 0.6),
Placebo	18.2 (5.7)	20.1 (3.1)	2.5 (4.8); (-2.6, 7.6),	p=0.093	p=0.086
ICP 06:00 (mmHg)					
Exenatide	16.1 (3.5)	16.2 (6.0)	0.6 (2.6); (-3.5, 4.8),	-5.9 (4.6); (-14.8, 3.1),	-5.0 (2.5); (-9.9, -0.2),
Placebo	18.2 (5.7)	22.1 (4.1)	3.1 (4.1); (-1.2, 7.4),	p=0.153	p=0.040

Overnight ICP monitoring. ICP, intracranial pressure.

FIGURE 14 - ICP OVERNIGHT RECORDING



ICP overnight recording. *ICP was continuously recorded overnight, graph shows mean (SEM) ICP values for exenatide and placebo groups.*

3.5.3.2. Initial 2.5-hour ICP time course

ICP reduces following acute administration of exenatide. ICP was significantly lower at both 90-120 minutes (-4.6 (2.1) (mean (SD)) mmHg p=0.028) and 120-150 minutes (-4.2 (2.1) (mean (SD)) mmHg, p=0.042). (Figure 15, table 11)

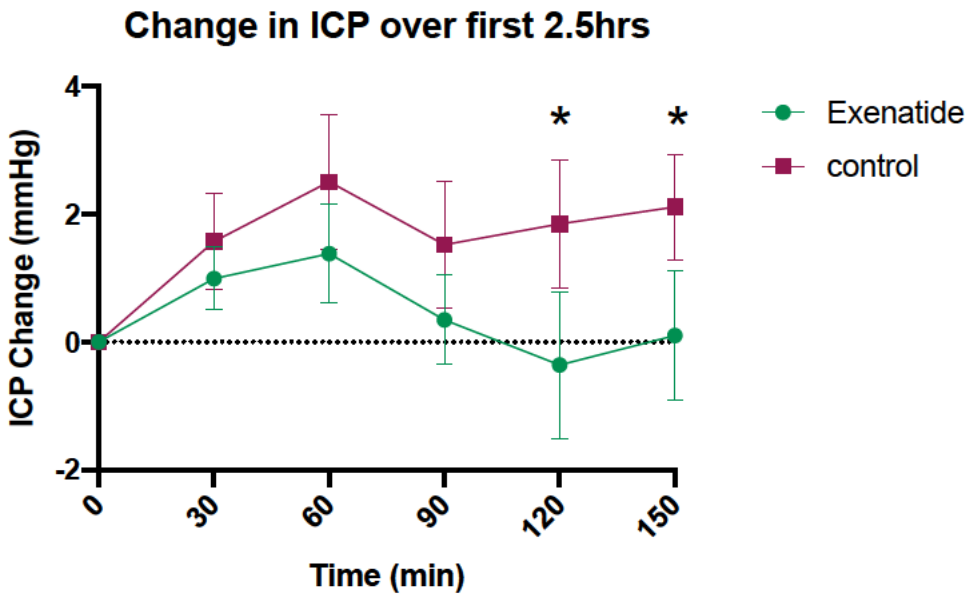
TABLE 11 - ICP OVER FIRST 2.5HRS

	Baseline	Time point	Difference baseline to time point	Difference between arms at time point	
				t-test	Hierarchical regression
	mean (SD)		mean (SD); 95%CI, p	mean (SE); 95%CI, p	mean (SE); 95%CI, p
ICP 0-30 mins (mmHg)					
Exenatide	22.3 (3.6)	23.3 (4.1)	1.0 (1.3); (-0.2, 2.2), p=0.089	-2.1 (2.4); (-6.8, 2.7), p=0.357	-2.3 (2.1); (-6.3, 1.8), p=0.274
Placebo	24.6 (4.1)	25.4 (4.0)	1.6 (2.0); (-.03, 3.4), p=0.080		
ICP 30-60 mins (mmHg)					
Exenatide	22.3 (3.6)	23.7 (4.9)	1.4 (2.1); (-0.5, 3.3), p=0.125	-2.6 (2.9); (-8.3, 3.0), p=0.330	-3.4 (2.1); (-7.5, 0.7), p=0.106
Placebo	24.6 (4.1)	26.3 (4.8)	2.5 (2.8); (-0.1, 5.1), p=0.055		
ICP 60-90 mins (mmHg)					
Exenatide	22.3 (3.6)	22.6 (4.7)	0.3 (1.9); (-1.4, 2.1), p=0.637	-2.7 (2.4); (-7.3, 2.0), p=0.226	-3.4 (2.1); (-7.5, 0.7), p=0.102
Placebo	24.6 (4.1)	25.3 (2.8)	1.5 (2.6); (-0.9, 3.9), p=0.174		
ICP 90-120 mins (mmHg)					
Exenatide	22.3 (3.6)	22.0 (3.8)	-0.4 (2.8); (-3.3, 2.6), p=0.769		

Placebo	24.6 (4.1)	25.7 (2.4)	1.8 (2.7); (-0.6, 4.3), p=0.116	-3.6 (2.1); (-7.8, 0.5), p=0.078	-4.6 (2.1); (-8.8, -0.5), p=0.028
ICP 120-150 mins (mmHg)					
Exenatide	22.3 (3.6)	21.8 (3.4)	-0.5 (1.9); (-2.3, 1.2), p=0.485	-4.2 (1.9); (-8.0, -0.4), p=0.031	-4.2 (2.1); (-8.3, -0.2), p=0.042
Placebo	24.6 (4.1)	26.0 (3.4)	1.4 (1.8); (-0.1, 2.9), p=0.060		

ICP monitoring, 2.5-hour time course. ICP, intracranial pressure. Due to the nature of hierarchical analysis, there is slight variation in values compared to those of the primary outcomes, however data included at timepoints is identical.

FIGURE 15 - CHANGE IN ICP OVER FIRST 2.5 HOURS



Change in ICP over first 2.5 hours. *ICP was continuously recorded over the first 2.5 hours of dosing, graph shows mean change (SEM) ICP values for exenatide and placebo groups compared to baseline.*

3.5.4. Secondary clinical outcomes

3.5.4.1. Headache

Following administration of the drug over the course of the 12 weeks the monthly headache days reduced significantly in the Exenatide arm, -7.7 (9.2) days (mean (SD), p=0.069 compared to the placebo arm -1.5 (4.8) days, p=0.404. There was no significant change in headache severity, Exenatide 0.5 (0.8) days, p=0.155, placebo -0.2 (1.8), p=0.782, or monthly analgesia days, Exenatide -0.9 (5.2) days, p=0.680, placebo 2.4 (5.1) days, p=0.254. (Table 12, Figure 16)

3.5.4.2. Vision

Visual acuity significantly improved in the exenatide arm compared to the Placebo arm -0.1 (0.06) logMar units, p=0.044. There was no significant change in perimetric mean deviation in the Exenatide arm -0.3 (1.1)dB, p=0.472, whilst the placebo arm improved 0.7 (0.7)dB, p=0.020. OCT RNFL did not change significantly in either arm, Exenatide -21.0 (28.8)μm, p=0.134 placebo -10.8 (88.0) μm, p=0.740. (Table 12, Figure 17)

3.5.4.3. Quality of life

No significant changes were seen in quality of life measured by SF-36 questionnaire in either the physical or mental component scores. Headache disability measured by HIT-6 was significantly higher in the Exenatide arm at baseline 62.9 (3.2) vs 55.8 (6.9), (mean (SD)), p=0.041, there was no significant change over the course of the trial. (Table 12)

3.5.4.4. BMI

There was no significant change in BMI in either Exenatide or placebo arm over the course of the trial, p=0.859. (Table 12, Figure 17)

TABLE 12 - SECONDARY OUTCOME MEASURES

	Baseline	**12 weeks**	**Difference baseline to 12 weeks**	**Difference between arms at 12 weeks**	
				t-test	Hierarchical regression
	mean (SD), n		mean (SD); 95%CI, p	mean (SE); 95%CI, p	mean (SE); 95%CI, p
Monthly headache days					
Exenatide	21.6 (5.2), n=7	13.9 (7.2), n=7	-7.7 (9.2); (-16.3, 0.8), p=0.069	5.1 (4.4); (-3.4, 13.6), p=0.218	5.1 (3.9); (-2.4, 12.7), p=0.184
Placebo	10.3 (8.5), n=8	8.8 (8.0), n=8	-1.5 (4.8); (-5.5, 2.5), p=0.404		
Monthly analgesic frequency					
Exenatide	7.9 (4.5), n=7	7.0 (5.7), n=7	-0.9 (5.2); (-5.7, 4.0), p=0.680	1.1 (3.2); (-5.2, 7.5), p=0.701	1.1 (2.5); (-3.8, 6.0), p=0.648
Placebo	3.4 (2.8), n=7	5.9 (5.2), n=7	2.4 (5.1); (-2.3, 7.1), p=0.254		
Headache severity (VRS 0-10)					

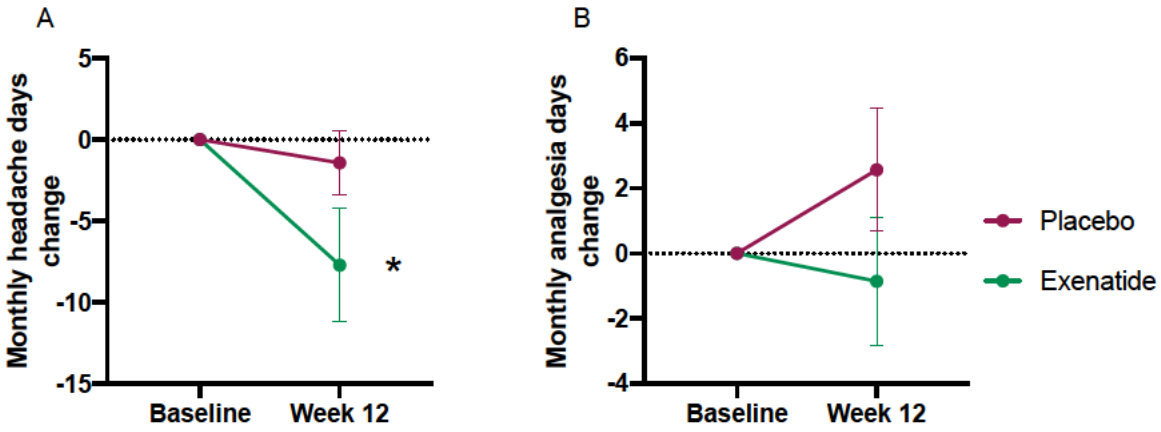
Exenatide	5.3 (1.1), n=7	5.8 (1.5), n=7	0.5 (0.8); (-0.2, 1.2), p=0.155		
Placebo	3.4 (2.5), n=8	3.3 (3.0), n=8	-0.2 (1.8); (-1.7, 1.3), p=0.782	2.5 (1.4); (-0.1, 5.2), p=0.060	2.5 (1.2); (0.3, 4.8), p=0.028
LogMar visual acuity					
Exenatide	0.0 (0.05), n=7	-0.1 (0.07), n=7	-0.1 (0.04); (-0.1, 0.0), p=0.004		
Placebo	0.0 (0.14), n=8	0.0 (0.12), n=8	0.0 (0.14); (-0.1, 0.1), p=0.921	-0.1 (0.06); (-0.2, 0.0), p=0.044	-0.1 (0.05); (-0.2, -0.1), p=0.036
Perimetric mean deviation worst eye dB (HVF 24-2 sita standard)					
Exenatide	-0.6 (1.0), n=7	-1.0 (0.9), n=7	-0.3 (1.1); (-1.4, 0.7), p=0.472		
Placebo	-2.7 (1.9), n=8	-2.0 (1.6), n=8	0.7 (0.7); (0.1, 1.3), p=0.020	1.0 (0.7); (-0.5, 2.5), p=0.162	1.0 (0.8); (-0.5, 2.5), p=0.188
Optical Coherence Tomography					

RNFL worst eye (um)					
Exenatide	153 (58.9), n=6	132 (34.0), n=6	-21.0 (28.8); (-51.2, 9.2), p=0.134	-40.2 (49.4); (-137.1, 56.7), p=0.371	-40.2 (47.2); (-133.0, 52.4), p=0.396
Placebo	183 (100.0), n=8	172 (114.0), n=8	-10.8 (88.0); (-84.3, 62.8), p=0.740		
Headache disability (HIT-6)					
Exenatide	62.9 (3.2), n=7	63.8 (6.8), n=5	1.8 (4.8); (-4.2, 7.8), p=0.450	10.4 (5.4); (-0.2, 21.2), p=0.055	11.0 (4.0); (3.1, 19.0), p=0.006
Placebo	55.8 (6.9), n=8	53.4 (10.6), n=8	-2.4 (6.2); (-7.5, 2.8), p=0.312		
Quality of Life (SF-36) PCS summary					
Exenatide	49.7 (20.3), n=7	53.8 (23.4), n=7	4.1 (7.4); (-2.7, 10.9), p=0.191	-5.7 (11.4); (-27.9, 16.6), p=0.576	-5.7 (9.5); (-24.3, 12.9), p=0.550
Placebo	57.8 (16.9), n=8	59.5 (11.8), n=8	1.7 (9.5); (-6.2, 9.6), p=0.632		

Quality of Life (SF-36) MCS summary					
Exenatide	43.4 (23.3), n=7	44.8 (24.2), n=7	1.4 (8.3); (-7.3, 10.1), p=0.692	-2.2 (13.0); -27.7, 23.4), p=0.845	-2.3 (10.3); (-22.5, 18.0), p=0.826
Placebo	46.6 (17.2), n=8	46.9 (10.5), n=8	0.5 (16.3); (-14.6, 15.5), p=0.940		
BMI (kg/m2)					
Exenatide	37.6 (7.9), n=7	37.5 (7.4), n=7	-0.1 (0.8); (-0.8, 0.7), p=0.851	-0.6 (3.7); (-7.9, 6.7), p=0.859	-0.6 (3.3); (-7.0, 5.8), p=0.854
Placebo	38.6 (4.7), n=8	38.1 (4.9), n=8	-0.5 (1.3); (-1.6, 0.6), p=0.336		

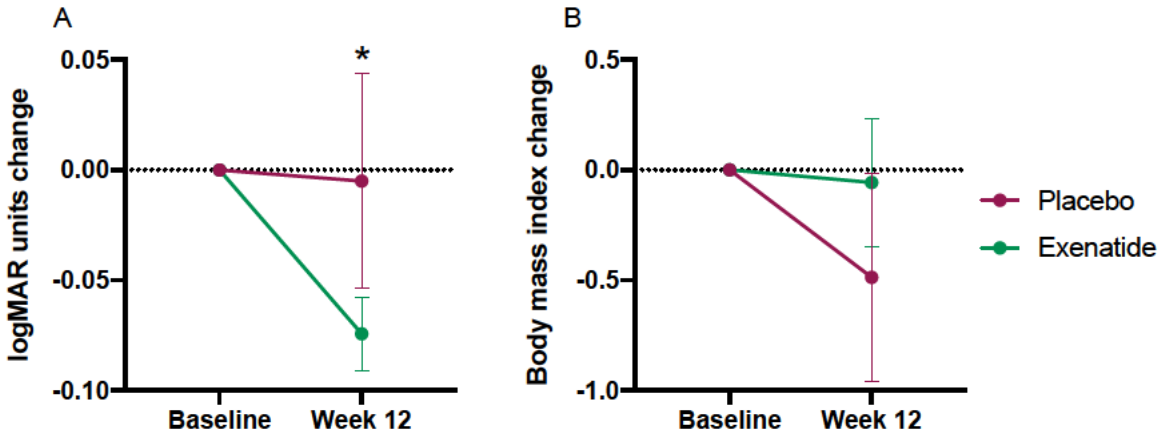
Secondary and exploratory outcomes. VRS, verbal rating scale; HVF, Humphrey visual field; RNFL, retinal nerve fibre layer; HIT-6, headache impact test 6, SF-36, short form 36; PCS, physical component score; MCS, mental component score; BMI, body mass index.

FIGURE 16 - CHANGE IN MONTHLY HEADACHE AND ANALGESIC DAYS



Change in monthly headache and analgesic days. *Mean monthly headache and analgesic days were recorded by 1 month diary prior to baseline and 12 weeks. Graphs show A) change in mean monthly headache days and B) change in mean monthly analgesic days (mean (SEM)).*

FIGURE 17 - CHANGE IN VISUAL ACUITY AND BMI



Change in visual acuity and BMI. Visual acuity and BMI were recorded at baseline and 12 weeks. Graphs show A) change in visual acuity (logMAR mean (SEM) and B) change in BMI (kg/m^2 mean (SEM)).

3.5.5. Exploratory clinical outcomes

3.5.5.1. Intraocular pressure

There was no significant change in intraocular pressure (mean of both eyes) between arms at 12 weeks, p=0.910. (Table 13)

TABLE 13 - INTRAOCULAR PRESSURE (MEAN BOTH EYES)

	Baseline	12 weeks	Difference baseline to 12 weeks	Difference between arms at 12 weeks	
				t-test	Hierarchical regression
	mean (SD), n		mean (SD); 95%CI, p	mean (SE); 95%CI, p	mean (SE); 95%CI, p
Intraocular pressure (mmHg)					
Exenatide	18.0 (2.0), n=7	16.9 (1.7), n=7	-1.2 (2.8); (-3.8, 1.4), p=0.306	0.0 (1.1); (-2.1, 2.1), p=0.994	-0.1 (1.1); (-2.3, 2.1), p=0.910
Placebo	16.7 (2.6), n=8	16.9 (1.9), n=7	0.5 (1.3); (-0.7, 1.7), p=0.375		

Exploratory outcomes – intraocular pressure. SD, standard deviation; SE, standard error; CI, confidence interval.

3.5.6. Drug concentration

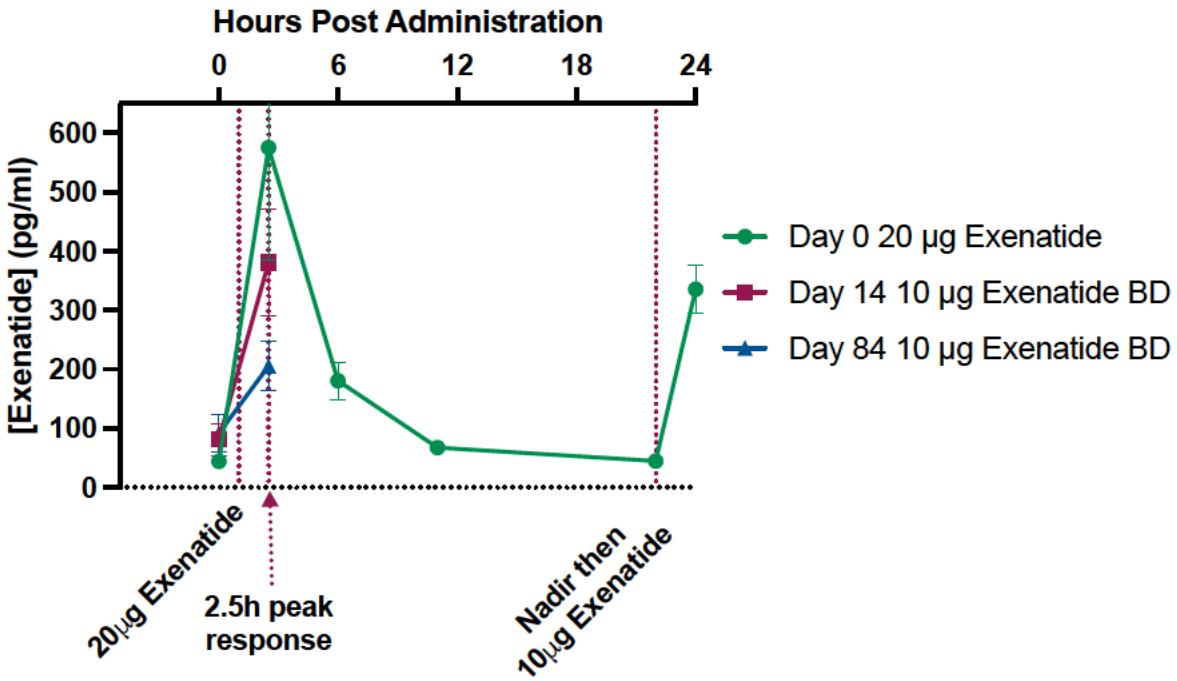
At baseline, week 2 and week 12, there was a sharp increase in Exenatide concentrations in patient serum 2.5 hours following subcutaneous administration of Exenatide. This was followed by a sharp decline in the peptide concentrations at 6 hours. The mean Exenatide concentrations which peak at 2.5 hours are lower at week 2 and week 12 than at baseline (380.67, 205.45 and 575.37 pg/ml respectively), which is expected as 20 µg of Exenatide was administered at baseline, compared to 10 µg administered at the week 2 and 12. (Table 14 Drug Concentrations, Figure 18)

TABLE 14 - EXENATIDE CONCENTRATIONS

Timepoint (Hrs) post-drug administration	Day 0 (20µg Exenatide) mean (SD) pg/ml	Day 14 (10µg Exenatide) mean (SD) pg/ml	Day 84 (10µg Exenatide) mean (SD) pg/ml
0	44 (12)	81 (55)	92 (62)
2.5	445 (128)	381 (180)	205 (83)
6	181 (85)		
11	67 (23)		
Day 1 pre - dose	45 (17)		
Day 1 2.5hrs post dose	336 (107)		

Exenatide serum concentration. SD, standard deviation; SE, standard error; CI, confidence interval.

FIGURE 18 - EXENATIDE DRUG CONCENTRATIONS



***Exenatide drug concentrations**. Serum exenatide concentrations were measured at baseline and 2.5-hours at Day 0, Day 14 and Day 84, on Day 0 measurements were additionally taken at 6 and 11-hours, and pre-Day 1 administration and at 2.5-hours. Graphs show serum exenatide concentration (pg/ml).*

3.5.7. Safety bloods

No significant changes were seen in liver function, renal function, lipids, cholesterol or HbA1C. (Table 15)

TABLE 15 - SAFETY BLOOD TEST RESULTS

	Baseline	12 weeks	Difference baseline to:	Difference between arms at 12 weeks	
			12 weeks	t-test	Hierarchical regression
	mean (SD), n		mean (SD); 95%CI, p	mean (SE); 95%CI, p	mean (SE); 95%CI, p
Creatinine (µmol/L)					
Exenatide	67.6 (9.5), n=7	72.7 (3.5), n=7	5.1 (7.4); (-1.7, 12.0), p=0.117		
Placebo	66.4 (8.1), n=8	67.1 (9.7), n=8	0.8 (7.0); (-5.1, 6.6), p=0.770	5.6 (4.2); (-2.7, 13.9), p=0.163	5.6 (4.2); (-2.7, 13.9), p=0.186
Alanine transaminase (IU/L)					
Exenatide	27.2 (13.9), n=6	24.9 (17.2), n=7	-0.2 (7.9); (-8.4, 8.1), p=0.961		
Placebo	21.3 (11.7), n=8	16.8 (5.4), n=8	-4.4 (7.3); (-10.5, 1.7), p=0.134	7.9 (8.2); (-8.1, 24.0), p=0.278	8.0 (6.5); (-4.7, 20.7), p=0.218
High density lipoprotein (mmol/L)					
Exenatide	1.3 (0.4), n=7	1.2 (0.2), n=7	0.0 (0.3); (-0.3, 0.2), p=0.710	-0.2 (0.1); (-0.5, 0.0), p=0.077	-0.2 (0.1); (-0.5, 0.0), p=0.088

Placebo	1.5 (0.2), n=8	1.5 (0.3), n=8	0.0 (0.2); (-0.2, 0.2), p=0.866		
Cholesterol (mmol/L)					
Exenatide	4.5 (0.8), n=7	4.7 (1.0), n=7	0.2 (0.6); (-0.4, 0.7), p=0.472		
Placebo	4.8 (1.0), n=8	4.7 (1.4), n=8	-0.1 (0.7); (-0.6, 0.5), p=0.715	0.0 (0.7); (-1.3, 1.4), p=0.968	0.0 (0.6); (-1.1, 1.1), p=0.964
Triglycerides (mmol/L)					
Exenatide	1.3 (0.6), n=7	1.3 (0.5), n=7	0.1 (0.5); (-0.4, 0.6), p=0.680		
Placebo	1.1 (0.2), n=8	1.2 (0.4), n=7	0.0 (0.4); (-0.3, 0.4), p=0.782	0.2 (0.3); (-0.4, 0.7), p=0.269	0.2 (0.2); (-0.3, 0.6), p=0.488
HbA1c (mmol/mol)					
Exenatide	35.4 (2.7), n=5	36.3 (2.9), n=7	1.0 (1.4); (-0.8, 2.8), p=0.189		
Placebo	35.0 (3.9), n=6	34.5 (3.0), n=8	0.7 (2.7); (-2.2, 3.5), p=0.576	1.8 (1.7); (-1.5, 5.1), p=0.259	1.8 (1.6); (-1.4, 5.0), p=0.278

Blood test results. HbA1C, glycated haemoglobin. *SD, standard deviation; SE, standard error; CI, confidence interval.*

3.5.8. Adverse events

One participant was withdrawn from the study prior to randomisation, this participant suffered a deterioration of their IIH requiring neurosurgical intervention with CSF diversion (Figure 18 consort). Following placement of the telemetric ICP monitors three participants developed minor post-operative wound infections that required a course of antibiotics and one participant reported wound swelling. During the course of the study there was one serious adverse event recorded that was unrelated to the study intervention: this was a diagnosis of thyrotoxicosis in a participant in the placebo arm. The most common adverse event was nausea reported in all participants of the Exenatide arm, three of which required treatment with anti-emetics. Nausea is a known side-effect of Exenatide.[143] (Table 16)

TABLE 16 - ADVERSE EVENTS

	Event	**Arm, n**
Serious adverse events	Thyrotoxicosis	Placebo, 1, - unrelated
Adverse events	Nausea treated	Exenatide, 3
	Nausea untreated	Exenatide, 4
	Minor wound infection	Exenatide, 2 Placebo 1
	Post-op wound swelling	Placebo, 1
Withdrawals	Clinical deterioration IIH	Exenatide, 1, (pre randomization)

Adverse events.

3.6. Discussion

This is the first randomised clinical trial to have investigated the biological effect of Exenatide on ICP in a cohort of patients with active IIH. The study has demonstrated that Exenatide reduces ICP with both single and repeated administration. Furthermore, the study has shown that Exenatide significantly reduced mean monthly headache days and improved visual acuity and that these effects were independent of weight loss.

IIH is a chronic disabling disease with intermittent relapses.[1] Raised ICP (≥25 cm CSF) represents the hallmark of IIH driving the consequent clinical sequelae, such as headache and papilloedema. In a previous study, a very low-energy diet (≤ 425 kcal/day) for three months induced 15% weight loss, this lowered the ICP significantly (mean 8.0 (SD 4.2) cm CSF, P<0.001). Over the course of the study improvements in papilloedema and visual function, and decreased headache frequency and severity with concomitant reduction in analgesic use were noted.[56] ICP reduction therefore drives disease remission in IIH with papilloedema resolution, and improvement in headache outcomes.

In this study, following administration of Exenatide, the reduction in ICP was 4.2 (1.9) (mean (SD)) mmHg, p=0.031 at 2.5 hours, 4.7 (2.1) mmHg, p=0.030 at 24 hours and 4.6 (2.5) mmHg, p=0.058 at 12 weeks.

This is the first trial to our knowledge to utilise telemetric monitors to measure ICP in IIH, this has allowed detailed characterisation of ICP changes and the ability to measure ICP for prolonged periods over several weeks without further invasive procedures, such as multiple lumbar punctures. This technology has led to the accurate demonstration of ICP lowering both with single dosing and with

repeated dosing. The intracranial telemetric monitors were safe, with only one failing to register by 12 weeks.

Existing treatments for IIH include weight management[56, 57] and pharmacotherapy.[53, 54] Acetazolamide, a carbonic anhydrase inhibitor, is the main pharmacological therapy used in IIH. Class I evidence exists for its use in IIH, and two RCTs have examined its efficacy.[54, 101] In 2014, a large randomised double-blind placebo-controlled study of acetazolamide combined with a low-sodium diet was published.[101] The IIH Treatment Trial (IIHTT) showed that the mean change in perimetric mean deviation (PMD) was statistically significantly better for those with mild visual loss using a low-calorie diet and acetazolamide compared to a low-calorie diet and placebo, after 6 months of treatment. In the IIHTT, the benefits were most marked in those with the most significant papilloedema. The study assessed ICP at baseline and 6 months with lumbar puncture, the study demonstrated a mean difference of -59.9 mmH_2O (-96.6 to -23.4)(95% confidence interval) favouring the acetazolamide group. Whilst there were limitations on the reporting of the ICP data (only 85 participants agreed to lumbar puncture at 6 months and the analysis utilised multiple imputation to account for missing data) it recognises that reduction of ICP is key for disease remission. High doses of acetazolamide were used in the IIHTT, with more than 40% of patients treated with 4000mg of acetazolamide daily. This dose may not be tolerable in a real-world setting, as previous studies have demonstrated that 48% of patients discontinue acetazolamide when daily doses of 1500mg are used.[144]

In the other randomised controlled trial 25 women with active IIH were randomised to receive acetazolamide and 25 to the placebo arm.[54] This study did not report CSF pressure.

Markey et al. reported a randomised, double blind placebo-controlled trial of AZD4017, in this study ICP was also assessed with lumbar puncture, there was a reduction in CSF pressure at 12 weeks, adjusted mean difference of -2.8cmH_2O (-7.1-1.5) p=0.2 with an exploratory analysis showing a significant in-group effect in the AZD4017 arm, -4.3cmH_2O (SD=5.7) p=0.009.[80]

GLP-1 agonists have a good safety record.[145] This study showed no change in renal or liver function. Previous studies of GLP-1 agonists have shown beneficial effects on metabolism and insulin sensitivity,[146] no changes were detected in this early phase short duration study which was not powered to detect these changes. GLP-1 agonists are well tolerated drugs, the most common side-effect of which is nausea following introduction; as such they may well be more acceptable to IIH patients in comparison to acetazolamide with more severe and common side-effects that often lead to limiting dose or withdrawal. GLP-1 agonists are known to induce weight loss, this effect was not seen in this short study although this would be expected to be beneficial in the IIH population, the majority of which suffer from obesity.

Clinical benefits were noted in terms of headache symptoms and visual function. Despite this being an early phase study, we were able to demonstrate a reduction in mean monthly headache days. The reduction of 7.7 days as well as being statistically significant is also highly clinically significant. In the wider headache literature, a reduction of 2 days per month following a treatment intervention is thought to show a benefit.[147] It should be noted however that there was no stratification by mean monthly headache days and the active arm had significantly more headache days at baseline. Headache is a key symptom of IIH leading to significant disability and reduction of quality of life[11],

the positive effects demonstrated in reduction in monthly headache days require further confirmation in an adequately powered RCT. IIH leads to significant visual loss in a small proportion of patients. This study noted a statistically significant improvement in visual acuity, measured by LogMar chart, between the trial arms at 12 weeks. Whilst the magnitude of this improvement is difficult to assess (5 letter improvement, equivalent to a line on a visual acuity chart), the minimally important clinical change for visual acuity has not yet been determined. There was no significant weight loss observed in this study, this indicates that the effects measured were independent of weight change.

This study has several limitations. As an early phase study, it was powered to the primary endpoints of ICP reduction single and with repeated dosing. As such the study was underpowered to detect differences in patient centred outcomes and the secondary clinical endpoints such as headache and visual field perimetry. Powering the study for those endpoints would have required a minimum 10-fold increase in participants; utilisation of telemetric ICP monitors would be unfeasible in such a larger study. Furthermore, no stratification was used in randomisation, promoting the generalisability of the study, however, groups were unmatched in baseline headache days and visual field perimetry, additionally patients with minimal visual field defects were not excluded as in prior studies thus making visual effects more difficult to detect, but promoting the clinical generalisability of the findings.

The results of this study may have wide reaching implications for other neurological disease, given the tolerability of Exenatide and its direct effect on ICP. The mechanism for the effect of GLP-1 agonists is thought to be reduction of CSF secretion by the choroid plexus.[96] This is not specific to IIH and therefore GLP-1 agonists may have a role in other conditions of raised ICP. In addition GLP-1

agonists are proposed to have neuro-protective properties making application to such conditions as traumatic brain injury tantalising.[148]

More widely raised ICP is encountered in a variety of acute conditions including traumatic brain injury, in these settings mannitol, hypertonic saline and narcotics are used to reduce ICP, however these medications and techniques exhibit short term effects.[63, 149, 150]

3.7. Conclusions

In this randomised controlled trial Exenatide significantly reduced ICP both acutely and during chronic dosing. Monthly headache days and visual acuity significantly improved in the exenatide group, and the effects were not mediated by weight loss. This is this first trial of a new drug treatment for IIH that has demonstrated a significant reduction in ICP, which was well tolerated. This evidence warrants further evaluation of Exenatide in a large RCT powered to evaluate clinically relevant outcome measures.

4. IIH Pressure Med Study

4.1. Introduction

Idiopathic Intracranial Hypertension (IIH) is characterised by increased intracranial pressure (ICP) with no identifiable cause. Recent weight gain is the major risk factor for development of the condition and its occurrence is most commonly observed in overweight women of reproductive age. [3, 11] The incidence of IIH is rising[137] and the incidence appears related to the prevalence of obesity.[4] Chronic disabling headaches occurs in the majority and there is a risk of blindness.[11] [138] Currently there is no licenced therapy for IIH: this is a clear unmet clinical need for patients, which was highlighted by a priority setting partnership.[12]

There is limited evidence for drug treatment in IIH with only 2 randomised, placebo-controlled trials of acetazolamide having been conducted to date.[53, 54] However a 2015 Cochrane review concluded that there was not enough evidence to recommend treatment with acetazolamide at that time.[58] Furthermore, several other drugs, including amiloride, furosemide, spironolactone and topiramate have been suggested as possible therapies for IIH or other conditions of raised intracranial pressure but with very limited evidence to date.

The aim of this study is to evaluate the effect on ICP and headache severity and frequency of acetazolamide, amiloride, furosemide, spironolactone and topiramate in a cohort of patients with IIH, utilising telemetric ICP monitoring.

4.2. Hypotheses

- I hypothesise that repeated administration of acetazolamide will reduce intracerebral pressure (ICP) and reduce headache frequency and severity.

- I hypothesise that repeated administration of amiloride will reduce intracerebral pressure (ICP) and reduce headache frequency and severity.

- I hypothesise that repeated administration of furosemide will reduce intracerebral pressure (ICP) and reduce headache frequency and severity.

- I hypothesise that repeated administration of spironolactone will reduce intracerebral pressure (ICP) and reduce headache frequency and severity.

- I hypothesise that repeated administration of topiramate will reduce intracerebral pressure (ICP) and reduce headache frequency and severity.

4.3. Aims

4.3.1. Primary aims

The aim of this randomised sequential trial was to assess the biological action of acetazolamide, amiloride, furosemide, spironolactone and topiramate on ICP.

4.3.2. Secondary aims

The secondary aims of the trial were to evaluate the clinical impact of lowering ICP by repeated dosing of acetazolamide, amiloride, furosemide, spironolactone and topiramate and what impact this would have on headache severity and frequency.

4.4. Methods

The IIH pressure study protocol, including the IIH Pressure Med sub-study is at section 8.

4.4.1. Study design summary

Design: The IIH Pressure Med study is a randomised, sequential, open label study of 5 drugs.

Setting: The study was conducted at the Clinical Research Facility, University Hospitals Birmingham NHS Trust.

Participants: All participants completing the IIH Pressure study were invited to participate in the IIH Pressure Med study.

Randomisation: List randomisation was used to assign order of medication rounds.

Blinding: The study was open label.

Drug doses: (see table 17) Drugs were taken for 2 weeks, where necessary drug doses were escalated after 1 week. If participants were unable to tolerate a medication due to side-effects a lower dose could be substituted.

Drug selection: for background see section 1.6. Drugs were selected on the basis of common usage in clinical practice and evidence of efficacy from clinical studies but do not represent an exhaustive list of all drugs that have been used in IIH.

Method: Participants attended for a baseline visit having completed a 7-day headache diary. ICP, headache, and cognition were assessed. Participants then took the assigned medication for 2 weeks prior to a repeat visit. Headache diaries were completed for 1 week prior to each visit. There was a minimum 1-week washout period between rounds.

Outcomes:

Primary: mean ICP in supine position over 30min

Secondary: mean monthly headache days, mean headache severity, cognition.

TABLE 17 - DRUG DOSES

Drug	Starting dose	Final dose
Acetazolamide	500mg BD	1G BD
Amiloride	10mg OD	10mg OD
Furosemide	40mg OD	80mg OD
Spironolactone	100mg OD	200mg OD
Topiramate	25mg BD 4 days, 25/50mg 3 days	50mg BD

Drug doses. OD, omni die; BD, bis die.

4.4.2. Telemetric ICP Catheter

Raumedic p-Tel ICP catheters were previously inserted into participants utilising standard clinical practise as described in section 8.11.

4.4.3. ICP recording and analysis

ICP was recorded continuously over 30 minutes at baseline and at 2 weeks with participants adopting a fully supine posture at 0° without additional head support. The raw data recording was then analysed by calculating mean ICP from the waveform for each block utilising proprietary software (Raumedic Dataview, Helmbrechts, Germany).

4.4.4. Headache

Daily headache diaries (appendix h, section 9) were completed for 1 week prior to each visit. Headache severity was recorded at each timepoint by a doctor trained in headache phenotyping. At baseline headache history and phenotype were recorded using the ICHD-3 criteria. Severity was assessed with a verbal rating scale 0-10 (10 most severe pain imaginable), duration (hours) and analgesic use were recorded.

4.4.5. Statistical methods

Eligible participants were randomized by a paper randomisation system administered by the Birmingham Clinical Trials Unit. The study analysis was conducted after the final visit of the final patient of the study. Data were analysed with R 4.0.0 (R foundation for statistical computing) and GraphPad Prism 8.0 (GraphPad Software), outcomes are summarised by means with standard deviations. Values at baseline are compared using t-tests. As an early phase study significance was set at p=<0.1. Missing data was excluded from the analysis.

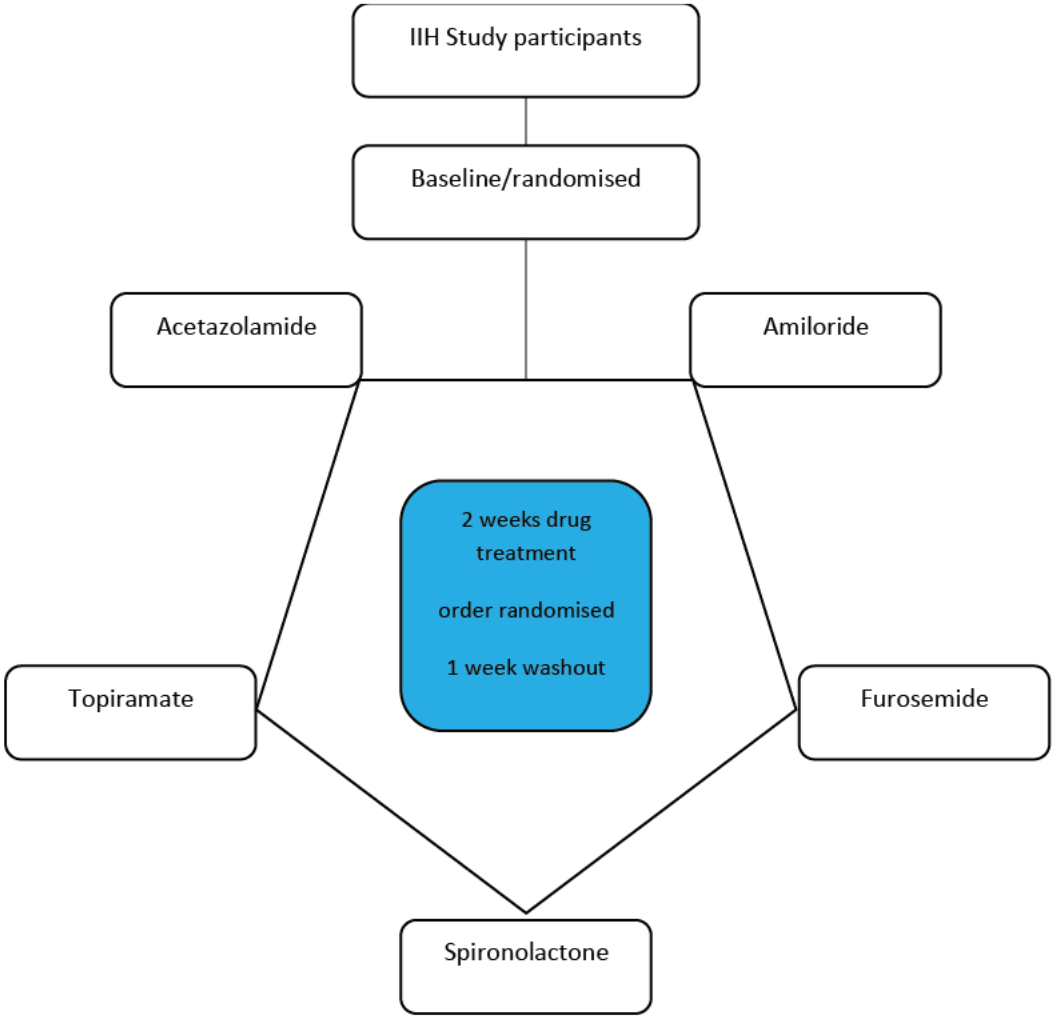
The response variable was change in ICP over the two-week assessment period. The outcome was analysed using a hierarchical regression model. The model included patient-level intercepts to reflect the within-patient serial correlation in outcomes. The model also included treatment as a factor variable at the population-level, to inform estimates of the treatment effects.

4.5. Results

4.5.1. Baseline characteristics

14 female patients enrolled to the IIH Pressure study were subsequently recruited to the IIH Pressure Med Study, consort diagram (figure 19). At study baseline mean (SD) age was 28 years (9), BMI 37.3 (7.0) kg/m2, ICP 24.4 (5.2) mmHg (equivalent to 33.2 cmCSF) and mean monthly headache days 15.1 (10.5). (Table 18)

FIGURE 19 - CONSORT DIAGRAM



Consort diagram. *Consort diagram describing the numbers and disposition of study subjects.*

TABLE 18 - BASELINE CHARACTERISTICS

	Mean (SD)
Number	14
Age	28 (9)
BMI (kg/m2)	37.3 (7.0)
ICP (mmHg) supine	24.4 (5.2)
ICP (cmCSF) supine	33.2 (7.1)
Headache	
Monthly headache days	15.1 (10.5)
Severity	5.2 (2.8)

Baseline characteristics. SD, standard deviation; BMI, body mass index; ICP, intracranial pressure; CSF, cerebrospinal fluid.

4.5.2. ICP change

Following 2 weeks treatment there was a fall in ICP recorded with all treatments apart from Amiloride. At 2 weeks ICP change (mean (SD)) for Acetazolamide was -3.3 (0.95) mmHg, p=0.0009, Amiloride -0.5 (0.88) mmHg, p=0.5592, Furosemide -3.0 (0.88) mmHg, p=0.0011, Spironolactone -2.7 (0.88) mmHg, p=0.0033 and Topiramate -2.3 (0.85), p=0.0095. (Table 19, Figure 20)

The treatment effects were analysed head-to-head for all treatment combinations, in this analysis no treatment showed a statistically significant effect over any other. (Table 20)

The magnitude of ICP reduction was correlated with increasing baseline ICP, the higher ICP was at baseline the higher the reduction in ICP, R^2=0.1172, p= 0.0139. (Figure 21)

TABLE 19 - IIH PRESSURE MED ICP CHANGE

Treatment	ICP pre (mmHg)	ICP post (mmHg)	n=	Mean change (SE) (mmHg)	Mean change (SE) (cmCSF)	Change (%)	p=
Acetazolamide	23.1	19.7	11	-3.3 (0.95)	-4.50 (1.3)	-14.52%	0.0009***
Amiloride	21.7	21.2	13	-0.5 (0.88)	-0.70 (1.2)	-2.53%	0.5592
Furosemide	24.5	21.5	13	-3.0 (0.88)	-4.12 (1.2)	-12.52%	0.0011**
Spironolactone	22.6	19.9	13	-2.7 (0.88)	-3.68 (1.2)	-12.10%	0.0033**
Topiramate	22.2	19.9	14	-2.3 (0.85)	-3.11 (1.2)	-10.29%	0.0095**

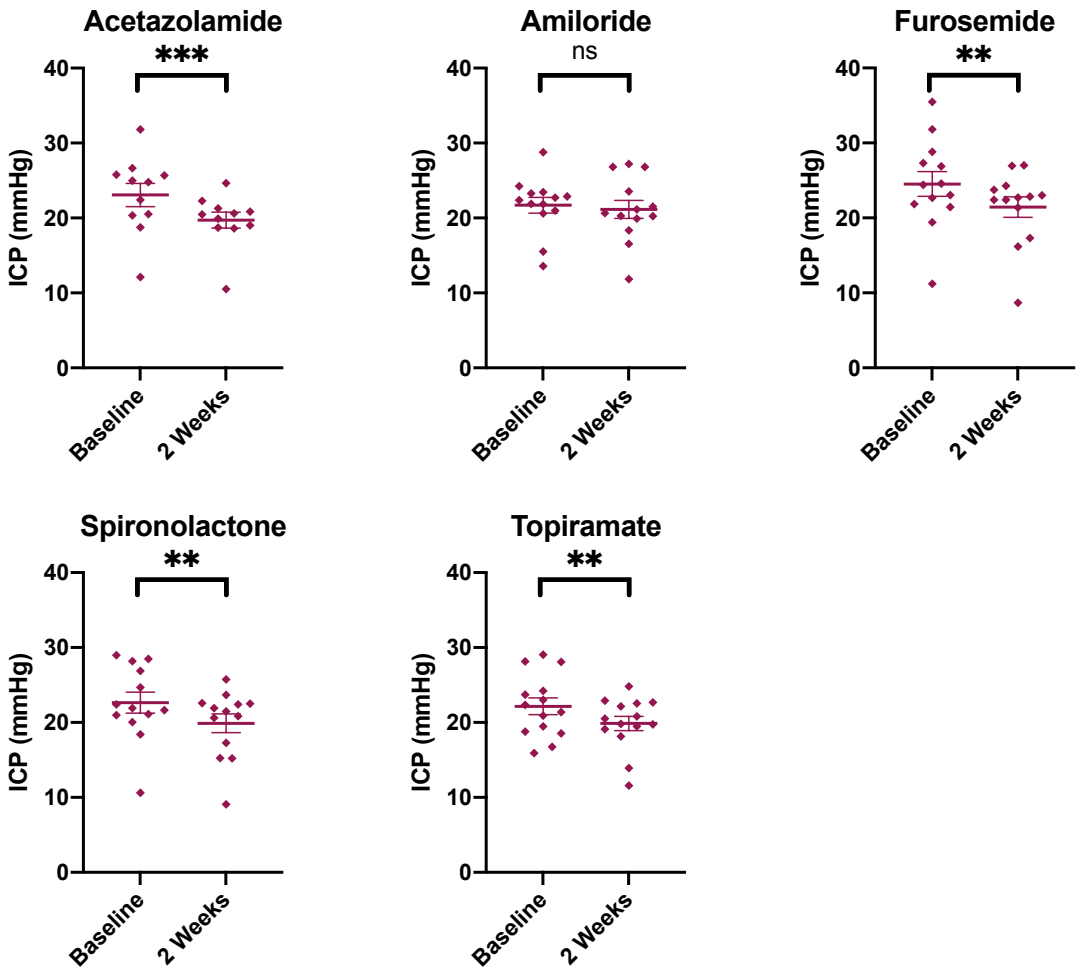
*IIH Pressure Med ICP change. ICP, intracranial pressure; SE, standard error. ** indicates p≤0.01, *** indicates p≤0.001.*

TABLE 20 - IIH PRESSURE MED ICP CHANGE TREATMENT COMPARISONS

Treatment comparisons	Mean change difference in ICP (SE) (mmHg)	p=
Acetazolamide vs Amiloride	-2.79 (1.15)	0.128
Acetazolamide vs Furosemide	-0.28 (1.16)	0.999
Acetazolamide vs Spironolactone	-0.60 (1.15)	0.985
Acetazolamide vs Topiramate	-1.02 (1.14)	0.897
Amiloride vs Furosemide	2.51 (1.11)	0.172
Amiloride vs Spironolactone	2.19 (1.10)	0.286
Amiloride vs Topiramate	1.77 (1.08)	0.483
Furosemide vs Spironolactone	-0.32 (1.11)	0.998
Furosemide vs Topiramate	-0.74 (1.08)	0.959
Spironolactone vs Topiramate	-0.42 (1.08)	0.995

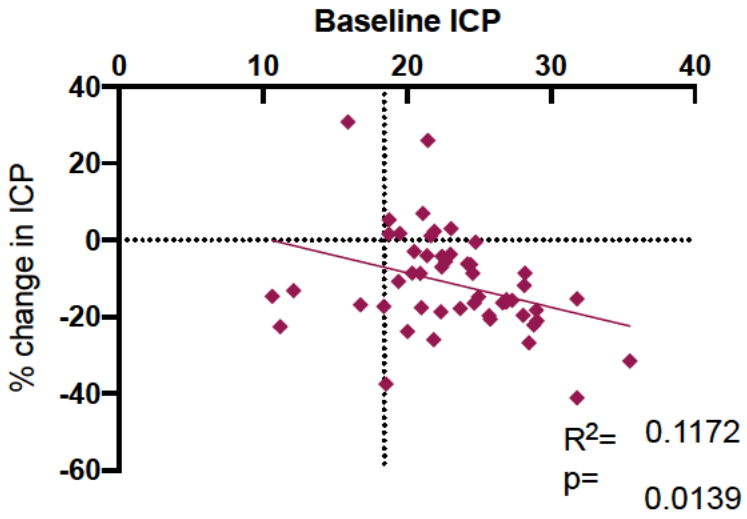
IIH Pressure Med ICP head-to-head. ICP, intracranial pressure; SE, standard error.

FIGURE 20- ICP PRE AND POST DRUG DOSING



ICP pre and post drug dosing. *ICP was recorded for 30 minutes supine before and after repeated drug dosing for 2 weeks. Graphs show pre and post ICP (mean (SE)) for Acetazolamide, Amiloride, Furosemide, Spironolactone and Topiramate.*

FIGURE 21 - REDUCTION IN ICP IS CORRELATED WITH BASELINE ICP



Reduction in ICP is correlated with baseline ICP*. ICP at baseline was compared to % change in ICP for all drugs that demonstrated a significant overall ICP change. Graph shows simple linear regression of baseline ICP compared to % change in ICP at 2 weeks.*

4.5.3. Headache

No significant changes were seen with any drug for headache frequency or severity by 2 weeks. (Table 21, Figure 22)

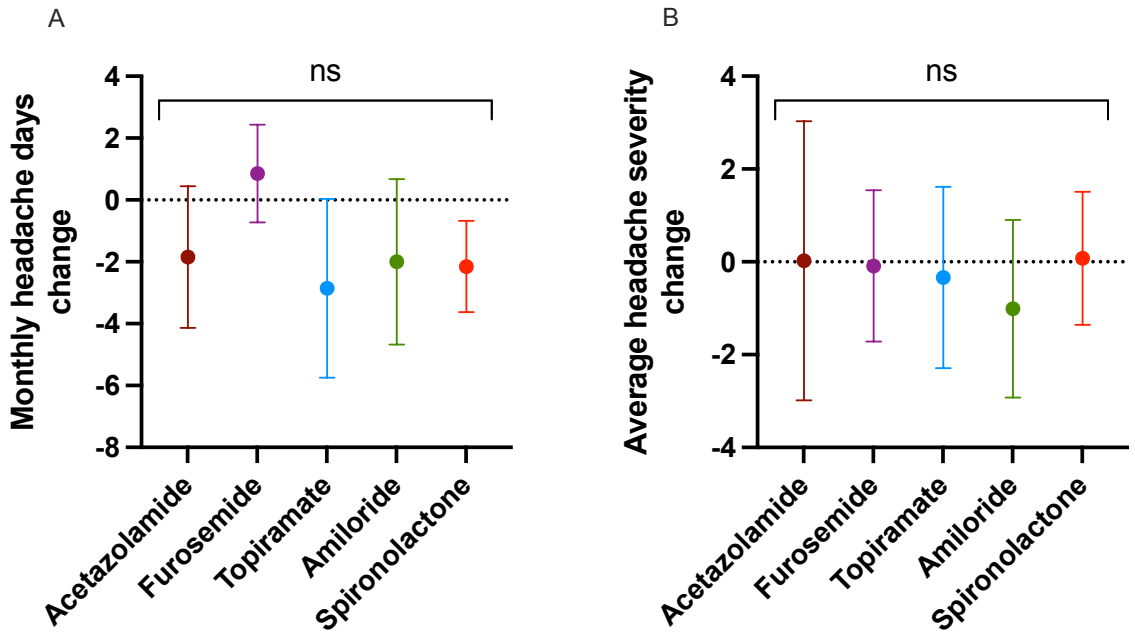
TABLE 21 - IIH PRESSURE MED HEADACHE SEVERITY AND MEAN MONTHLY HEADACHE DAYS CHANGE

Treatment		
Headache Severity	**Mean change (SE)**	**p=**
Acetazolamide	0.03 (0.60)	0.966

Amiloride	-1.01 (0.55)	0.072
Furosemide	-0.09 (0.55)	0.873
Spironolactone	0.09 (0.57)	0.889
Topiramate	-0.34 (0.55)	0.544
Headache Frequency	**Mean change (SE) (days)**	
Acetazolamide	-2.00 (2.44)	0.416
Amiloride	-2.00 (2.26)	0.379
Furosemide	0.86 (2.26)	0.706
Spironolactone	-2.15 (2.34	0.362
Topiramate	-2.86 (2.26)	0.211

IIH Pressure Med Headache outcomes. ICP, intracranial pressure; SE, standard error.

FIGURE 22 - CHANGE IN HEADACHE SEVERITY AND FREQUENCY



Change in headache severity and frequency. *Mean monthly headache days and mean severity were recorded by 7-day diaries at baseline and 2 weeks. Graphs show A) change in mean monthly headache days and B) change in average headache severity.*

4.5.4. Safety

There were no adverse events or serious adverse events reported during the IIH Pressure Med study. All telemeters functioned normally throughout the study.

Side-effects are reported in table 27, 6.5.2. The commonest side-effects were paraesthesia with acetazolamide, 100% and brain fog with topiramate 71%.

Some participants were unable to tolerate the maximum drug dosage, study dosages are reported in table 22. 2 participants had to reduce doses of acetazolamide, 1 took 500mg BD and 1 250mg BD for the final 7 days. 1 participant stopped taking spironolactone on day 10, 1 participant stopped taking topiramate on day 4.

TABLE 22 - DRUG DOSAGES

Drug	Drug dose per protocol (n=)	Reduced dose (n=)
Acetazolamide	9	2
Amiloride	13	0
Furosemide	13	0
Spironolactone	12	1
Topiramate	13	1

IIH Pressure Med drug doses.

4.6. Discussion

This is the first randomised sequential trial to investigate the biological effect of drugs commonly used in the treatment of IIH on ICP in a cohort of patients with active IIH. The study demonstrates that acetazolamide, furosemide, spironolactone and topiramate all significantly reduce ICP whilst amiloride has no significant effect. In head-to-head comparison acetazolamide, amiloride, furosemide, spironolactone and topiramate did not have significantly greater effects than each other. The magnitude of ICP reduction correlated with increasing baseline ICP, thus greater ICP reduction was seen in participants with higher starting ICP.

The effect of acetazolamide, amiloride, furosemide, spironolactone and topiramate on headache severity and frequency was assessed with no drug significantly reducing either, however this trial was not power for this analysis.

IIH is a chronic disease with intermittent relapses. Raised ICP (>25cmCSF) is the hallmark of the disease resulting in the common sequelae of headache and papilloedema. In a previous study, a very low-energy diet (≤ 425 kcal/day) for three months induced 15% weight loss, this lowered the ICP significantly (mean 8.0 (SD 4.2) cm CSF, P<0.001) compared to ICP measured in the same cohort after a 3-month period with no diet intervention. Over the course of the study papilloedema and visual function improved, and headache frequency and severity reduced.[56] ICP reduction therefore drives disease remission in IIH with papilloedema resolution, and improvement in headache outcomes.

In this study, following 2 weeks drug treatment, the reduction in ICP with acetazolamide was 3.3 (0.95) (mean (SE)) mmHg, p=0.0009, amiloride was 0.5 (0.88) mmHg, p=0.56, furosemide was 3.0

(0.88) mmHg, p=0.0011, spironolactone was 0.27 (0.88) mmHg, p=0.0033 and topiramate was -2.3 (0.85) mmHg, p=0.0095. No drug had significantly greater effects than each other in head-to-head analysis.

This is the first trial to our knowledge to utilise telemetric monitors to measure ICP in IIH. This has allowed detailed characterisation of ICP changes and the ability to measure ICP for prolonged periods over several weeks without further invasive procedures, such as multiple lumbar punctures. This technology has allowed this study to be the first to use a randomised sequential design to compare the efficacy of 5 commonly used drugs in a cohort of patients with IIH. The intracranial telemetric monitors were safe, with all monitors functioning throughout the duration of this study.

Existing treatments for IIH include weight management[56, 57] and pharmacotherapy.[53, 54] Acetazolamide, a carbonic anhydrase inhibitor, is the main pharmacological therapy used in IIH. Class I evidence exists for its use in IIH, and two RCTs have examined its efficacy [53, 54]. In 2014, a large randomised double-blind placebo-controlled study of acetazolamide combined with a low-sodium diet was published[53]. The IIH Treatment Trial (IIHTT) assessed ICP at baseline and 6 months with lumbar puncture, the study demonstrated a mean difference of -59.9 mmH_2O (-96.6 to -23.4) (95% confidence interval) favouring the acetazolamide group by 6-months. Whilst there were limitations on the reporting of the ICP data (only 85 participants agreed to lumbar puncture at 6 months and the analysis utilised multiple imputation to account for missing data) it recognises that reduction of ICP is key for disease remission. High doses of acetazolamide were used in the IIHTT, with more than 40% of patients treated with 4000mg of acetazolamide daily. This dose may not be tolerable in a real-world setting, as previous studies have demonstrated that 48% of patients discontinue acetazolamide when daily doses of 1500mg are used. [54]

Amiloride is a potassium sparing diuretic, it has been shown to reduce ICP in animal models via blockade of the Na+/H+ exchanger or Na+ channels,[59, 60] but there have not been any human studies thus far investigating its effect on ICP, although use in IIH is reported in a case series.[61]

Furosemide, a loop diuretic, has been used to treat IIH,[62] although there is evidence for reduction of ICP in other diseases in humans,[63] it has not previously been evaluated within a trial setting in IIH.

Spironolactone is also a potassium sparing diuretic commonly used in the settings of heart failure and hypertension. A study by Friedman et al. in 1998 assessed the effect of spironolactone along with chlorthalidone and sympathomimetic therapy on orthostatic oedema in IIH and matched control groups.[64] However the study was unable to formally assess clinically relevant outcomes or ICP. Additionally, spironolactone has been observed to control IIH symptoms in patients with IIH and primary aldosteronism in a case series.[61]

Topiramate is a sulfamate modified fructose diacetonide, originally developed as an anticonvulsant drug for the treatment of epilepsy. However, it has also been used for the treatment of migraine and for weight loss. Topiramate has several cellular targets including voltage gated sodium channels, GABA-A receptors, and carbonic anhydrase. It has similar inhibitory activity to acetazolamide of the Carbonic Anhydrase II and XII isoforms.[65]

Topiramate has class 1 evidence as prophylaxis in the treatment of migraine.[66-68] It also has well documented effects on weight loss.[69, 70] With weight loss known to be beneficial in the treatment of IIH[56] and headache one of the leading causes of morbidity in IIH, topiramate is of particular

interest as a potential therapy. A 2007 trial reported by *Celebisoy et al.* randomised 40 patients with IIH to treatment with topiramate or acetazolamide, they found significant improvements in visual fields in both groups, and no significant difference in treatment efficacy between the groups.[71]

This study has several limitations, as an exploratory sequential randomised study no control group was included, this was planned but abandoned following the COVID-19 pandemic. The study duration limited the dose escalation that was possible although all drugs were escalated to normal clinical doses during the 2-week dosing period. In addition, the 2-week dosing period may have been too short to realise any benefit in terms of headache measures. Apart from headache, clinically relevant outcome measures were not assessed. As an exploratory study it was not powered to detect differences between drugs or for secondary outcomes (headache severity and mean monthly headache days). Due to the study being underpowered to detect differences in effect between different drugs, mechanistic inferences cannot be sought.

The results of this may have implications for future study design suggesting similar efficacy in terms of ICP reduction across several drugs commonly used in the treatment of IIH, acetazolamide, furosemide, spironolactone and topiramate. Ideally future studies would be conducted and powered to detect significant differences between active treatments, this was the case with the IIH Intervention trial albeit comparing surgical and medication arms, the study was discontinued. However, it would be reasonable to consider active comparator arms in future phase 3 studies.

4.7. Conclusion

In this randomised, sequential, open-label trial ICP was significantly reduced by administration of acetazolamide, furosemide, spironolactone and topiramate. This trial was not designed (not powered) to assess clinically relevant outcomes. Amiloride had no significant effect on ICP. In head-to-head comparison no drug significantly reduced ICP compared to any other. This is the first trial to utilize telemetric ICP monitors and a sequential design to accurately assess the effect on ICP of several drugs in patients with IIH.

It is not clear if this reduction in ICP would impact on clinical measures. The duration of dosing to impact clinical measures is of future interest.

5. IIH Pressure Med Cognition

5.1. Introduction

Idiopathic Intracranial Hypertension (IIH) is characterized by increased intracranial pressure (ICP) with no identifiable cause. Recent weight gain is the major risk factor for development of the condition and its occurrence is most commonly observed in overweight women of reproductive age. [3, 11] The incidence of IIH is rising[137] and the incidence appears related to the prevalence of obesity.[4] Chronic disabling headaches occurs in the majority and there is a risk of blindness.[11] [138]

IIH patients commonly report symptoms of cognitive impairment[151] and formal assessment of cognitive performance has been performed in several small studies.[115, 152-155] The effect of treatment of IIH on cognitive performance has recently been assessed in the IIH Weight Trial[57] reported by *Grech et al*.[117]

The effects of drug treatment on cognition have not been assessed in IIH although the most commonly used drug for the treatment of IIH, acetazolamide, is known to impair cognitive performance.[118] Similarly topiramate also used in the treatment of IIH has well documented deleterious effects on cognition.[156]

5.2. Hypotheses

I hypothesise that administration of drugs commonly used to treat IIH may impair cognition in IIH.

5.3. Aims

5.3.1. Primary aims

- The study will assess cognitive performance in a cohort of patients with IIH.
- The study will assess the effect of acetazolamide, amiloride, furosemide, spironolactone, topiramate and exenatide on cognition.

5.3.2. Secondary aims

- The study will assess the potentially confounding effect of headache on cognition in IIH.

5.4. Methods

The IIH pressure study protocol, including the IIH Pressure Med sub-study is at section 8.

5.4.1. Study design summary

Design: The IIH Pressure Med study is a randomised, sequential, open label study of 5 drugs.

Setting: The study was conducted at the Clinical Research Facility, University Hospitals Birmingham NHS Trust.

Participants: All participants completing the IIH Pressure study were invited to participate in the IIH Pressure Med study.

Randomisation: List randomisation was used to assign order of medication rounds.

Blinding: the study was open label.

Drug doses: see table X. Drugs were taken for 2 weeks, where necessary drug doses were escalated after 1 week. If participants were unable to tolerate a medication due to side-effects a lower dose could be substituted.

Method: Participants attended for a baseline visit having completed a 7-day headache diary. ICP, headache, and cognition were assessed. Participants then took the assigned medication for 2 weeks prior to a repeat visit. Headache diaries were completed for 1 week prior to each visit. There was a minimum 1-week washout period between rounds.

Outcomes:

Primary: mean ICP in supine position over 30min

Secondary: mean monthly headache days, mean headache severity, cognition.

5.4.2. Cognitive testing battery

Detailed evaluation of cognition was undertaken utilising the NIH Toolbox Cognitive Battery (version 1.11).[157, 158] The battery consists of 7 standardised testing paradigms measuring different constructs. (Table 23) The battery is broadly used and consists of a standardised assessment covering a broad range of cognitive domains. It utilises a computer adaptive testing paradigm allowing

assessments to be completed in 40-minutes. The battery has been validated in a US population across a large normative population (4859 individuals) and a broad array of acquired brain injuries.[158] Test scores are expressed as fully corrected T-scores, (where a score of 50 is population mean and +/-10 is 1 standard deviation from mean) individual patient scores are corrected for age, gender, educational attainment, and ethnicity.

TABLE 23 - COGNITIVE TEST SUMMARY

Test	Cognitive domains
Flanker Inhibitory Control and Attention Test	attention and executive function
Picture Sequence Memory Test	episodic memory
List Sorting Working Memory Test	working memory
Picture Vocabulary Test	language
Oral Reading Recognition Test	language
Dimensional Change Card Sort Test	executive function
Pattern Comparison Processing Speed Test	processing speed

IIH Pressure cognitive battery summary.

The NIH Toolbox cognitive battery consists of seven tests. These contribute to 2 composite scores, crystalised and fluid.

The crystalised score is derived from the picture vocabulary test and the oral reading recognition test. Crystalised cognition or intelligence derives from knowledge accumulated through prior

learning and experiences. Fluid intelligence in contrast is the ability to think rapidly and reason to solve novel problems without reliance on past learning or experience. [159] Crystalised intelligence is resistant to change with aging and biological insult in contrast to fluid intelligence which has well described changes over life and with disease.[160, 161] The fluid composite score incorporates the flanker test, picture sequence and list sort memory tests, dimensional change card sort test and the pattern comparison processing speed test.

The picture vocabulary test measures receptive vocabulary. Participants select the picture that most closely matches the meaning of the word. The oral reading recognition test assesses reading decoding skill and crystallized abilities, the participant reads and pronounces letters and words as accurately as possible. These tests are both of language ability and measure crystalised intelligence.

The flanker test consists of a set of response inhibition tests. The target is flanked by decoy stimuli which are presented either congruently or incongruently with the target, accuracy and speed of target identification is recorded. The test measures the allocation of the participants' limited capacity to deal with environmental stimulation and most closely maps to the cognitive domains of attention and executive function.

The picture sequence memory test presents a number of pictures of activities to a participant in an order, the pictures are then randomised, and the subject asked to identify the correct order of presentation. This tests episodic memory.

The list sort working memory test presents the participant with up to 2 categories of items in a randomised order, the participant is required to recall the items by category and size, this tests working memory.

The dimension change card sort test presents the subject with 2 pictures which vary along

2 dimensions of shape and colour, they must match cards by a given dimension and accuracy and speed are recorded. This test predominantly assesses executive function.

The pattern comparison processing speed test presents 2 simple pictures which the subject has to indicate if they match or not. This tests the speed of information processing.

Tests were administered by a trained team member in a controlled, quiet environment under standard lighting conditions. Testing was performed at baseline and after 2 weeks of drug administration (in line with IIH Pressure Med Study visits). Exenatide was evaluated after 12 weeks (in line with IIH Pressure Study protocol).

5.4.3. Headache

Headache severity (verbal rating scale 0-10, 10 most severe pain imaginable) was recorded at baseline and 2 weeks at the beginning of administration of the cognitive testing battery. At baseline headache history and phenotype were recorded using the ICHD-3 criteria.[162]

5.4.4. Statistical methods

Eligible participants were randomized by a paper randomisation system administered by the Birmingham Clinical Trials Unit. The study analysis was conducted after the final visit of the final patient of the study. Cognitive performance of the participants was evaluated using fully corrected T-scores, these are corrected for age, sex, education and ethnicity.[163] Data were analysed with R 4.0.0 (R foundation for statistical computing) and GraphPad Prism 8.0 (GraphPad Software), outcomes are summarised by means with standard deviations. Values at baseline are compared using t-tests. As an early phase study significance was set at p=<0.1. Missing data was excluded from the analysis.

The response variable was change in cognition over the two-week assessment period. We analysed this outcome using a hierarchical regression model. The model included patient-level intercepts to reflect the within-patient serial correlation in outcomes. The model also included treatment as a factor variable at the population-level, to inform estimates of the treatment effects.

5.5. Results

5.5.1. Baseline characteristics

14 female patients enrolled to the IIH Pressure study were subsequently recruited to the IIH Pressure Med Study, consort diagram, figure 19, section 4.5.1. At study baseline mean (SD) age was 28years (9), BMI 37.3 (7.0) kg/m2, ICP 24.4 (5.2) mmHg (equivalent to 33.2 cmCSF) and mean monthly headache days 15.1 (10.5). (Table 24)

Cognitive testing was completed at baseline prior to any interventions. Cognitive performance of the participants was evaluated using fully corrected T-scores, these are corrected for age, sex, education, and ethnicity.[163] The participants demonstrated normal cognitive ability in the crystalised domains. However cognitive performance in the fluid domain was more than 1 standard deviation below expected, fully corrected T-Score (mean (SE)) 37.2 (2.55). Within the fluid domain performance was particularly reduced in the Flanker 33.9 (1.85) and dimension change paradigms 38.1 (3.77). The remaining fluid domains were reduced but not below 1 standard deviation. (Table 25, Figure 23)

TABLE 24 - BASELINE CHARACTERISTICS

	mean (SD)
N=	14
Age	28 (9)
BMI (kg/m2)	37.3 (7.0)
ICP (mmHg) supine	24.4 (5.2)

ICP (cmCSF) supine	33.2 (7.1)
Headache	
Monthly headache days	15.1 (10.5)
Severity	5.2 (2.8)

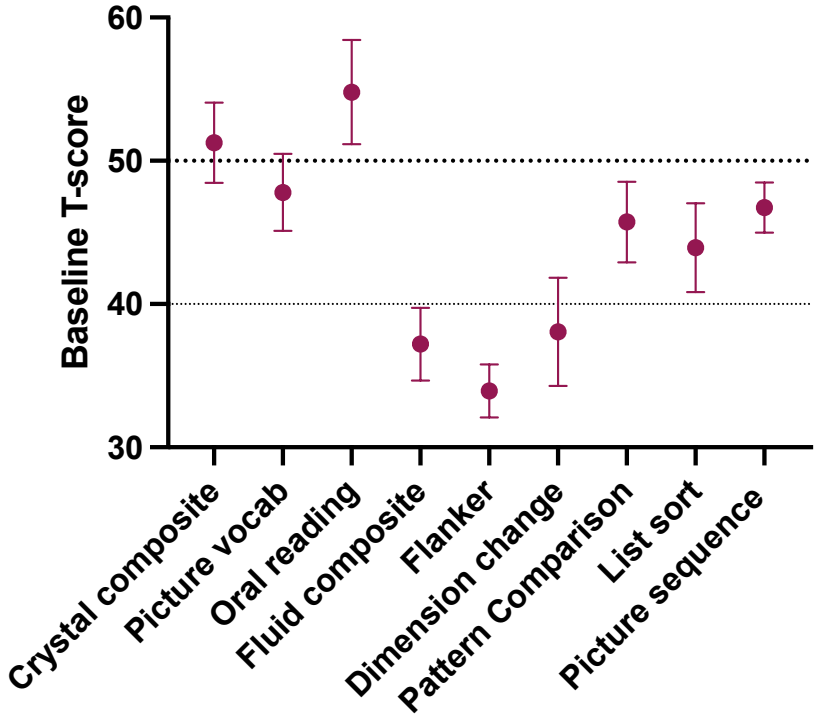
Baseline characteristics. SD, standard deviation; BMI, body mass index; ICP, intracranial pressure; CSF, cerebrospinal fluid.

TABLE 25 - BASELINE COGNITIVE SCORES

Cognitive test	**T-score mean (SE)**
Crystal composite	51.3 (2.80)
Picture vocab	47.8 (2.70)
Oral reading	54.8 (14.1)
Fluid composite	37.2 (2.55)
Flanker	33.9 (1.85)
Dimension change	38.1 (3.77)
Pattern Comparison	45.73 (2.81)
List sort	43.9 (3.09)
Picture sequence	46.73 (1.76)

Baseline cognitive scores. *Scores are shown as mean of fully corrected T-score. Fully corrected T-scores are corrected for participants age, educational background, gender and ethnicity. Population mean is 50, +/-10 is 1 standard deviation. SE, standard error.*

FIGURE 23 - BASELINE COGNITIVE SCORES



Baseline cognitive scores*. Cognitive testing was performed for all participants prior to intervention. Graph shows mean (SE) fully corrected T-Scores for each cognitive domain and crystalised and fluid composite scores, (T-score of 50 is population mean with 40 being 1 standard deviation below mean).*

5.5.2. Drug side-effects

Participants were asked to report side-effects following 2 weeks of receiving each medication. The most commonly reported side-effects were nausea (20 reports, 7 for exenatide) and paraesthesia (16 reports, 11 for acetazolamide). Cognitive disturbance was reported by 10 patients (71%) following topiramate but only 1 participant (9%) with acetazolamide, participants taking acetazolamide also reported paraesthesia 100%, dysgeusia 64%, nausea 55%. Lethargy was reported by 3 participants

with topiramate and 5 following acetazolamide. (Table 26). The drug with the least reported side-effects was amiloride.

TABLE 26 - REPORTED SIDE-EFFECTS

Symptom	Exenatide	Acetazolamide	Amiloride	Furosemide	Spironolactone	Topiramate
	n=7	n=11	n=13	n=13	n=13	n=14
Mood disturbance	0	1	0	0	0	4
Lethargy	0	5	0	0	2	3
Cognitive fog/memory	0	1	0	0	0	10
Paraesthesia	0	11	0	0	1	4
Visual disturbance	0	0	1	0	0	1
Coordination/balance	0	1	0	0	0	3
Palpitation	0	0	0	0	0	1
Nausea	7	6	0	4	1	2
GI upset	0	5	0	0	1	1
Taste disturbance	0	7	0	0	1	0
Diuresis	0	0	1	8	2	0
Menstrual disturbance	0	1	0	0	0	0
Dizziness	0	2	1	1	1	1
Muscle cramp	0	1	0	1	1	0
Headache	0	0	0	0	1	1
Thirst/dry mouth	0	0	2	0	1	1
Skin rash	0	0	0	0	2	0
Feel faint	0	0	0	2	1	0
Abdominal pain	0	0	1	1	0	0
Shortness of breath	0	3	0	0	0	0
Dry eyes	0	0	0	0	0	0
Sleep disturbance	0	0	0	0	0	1
Ankle swelling	0	0	0	1	0	0
Total	7	44	6	18	15	33

IIH Pressure Med reported side-effects by drug.

5.5.3. Cognition and drug effects

5.5.3.1. Exenatide

There was a significant increase in crystal composite score in the placebo group between baseline and week 12, mean difference of T-score (SD) 6.5 (7.6) p=0.046. Remaining scores in the crystalised domain for both exenatide and placebo were not statistically significant. There were significant increases in many scores in the fluid domain for both exenatide and placebo groups with fluid composite score (mean difference T-score (SD)), for exenatide 14.4 (5.6), p=0.0005 and placebo 12.1 (4.5), p=0.0001. There were no significant differences between arms at 12-weeks. (Table 27, Figure 24)

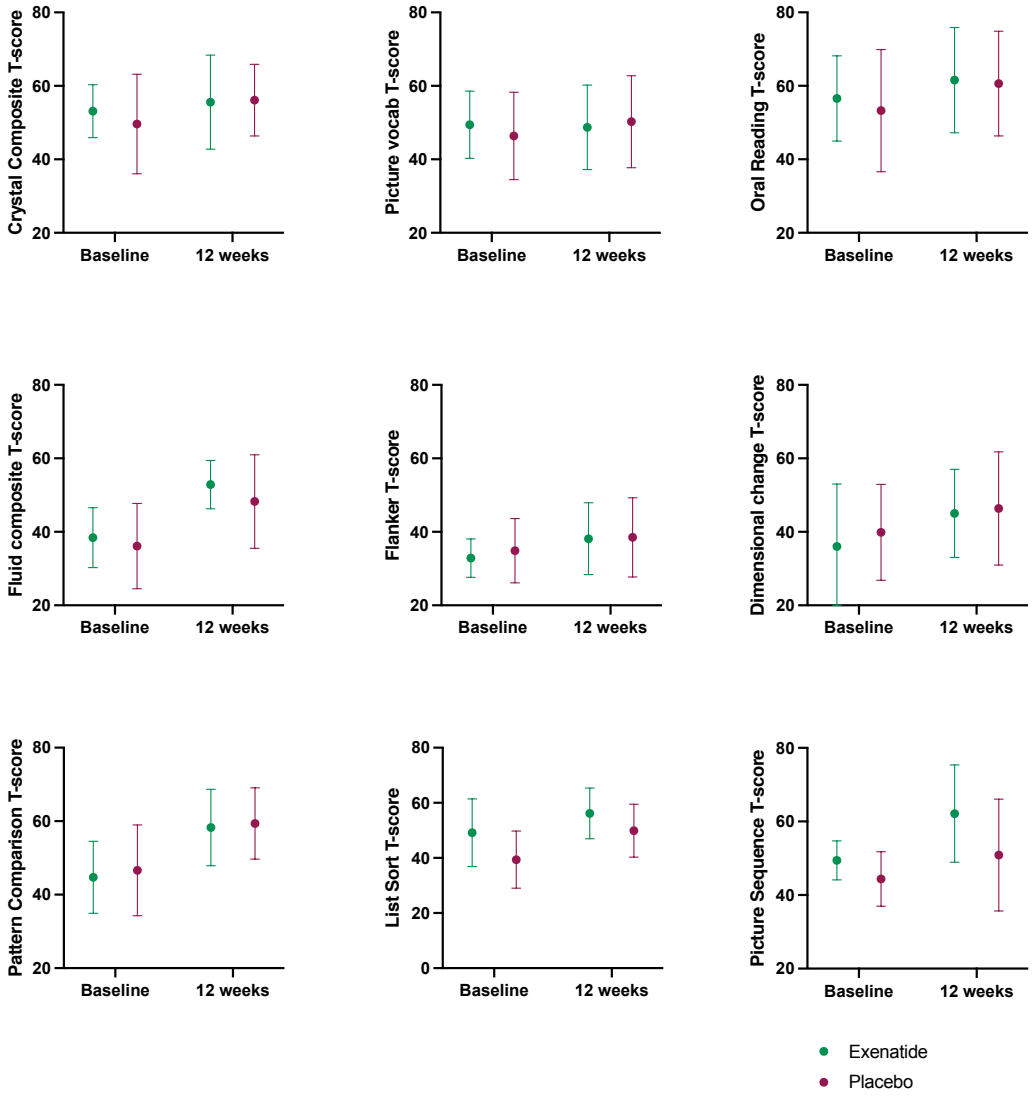
TABLE 27 - IIH PRESSURE COGNITIVE SCORES

		Baseline	**12 weeks**	**Difference baseline to time point**	**Difference between arms at 12 weeks**
					t-test
		mean (SD)		**mean (SD); 95%CI, p**	**mean (SE); 95%CI, p**
Cognition Crystalised					
Composite	Exenatide	53.1 (7.2)	55.6 (12.8)	2.4 (7.7); (-4.7, 9.6), p=0.436	
	Placebo	49.6 (13.6)	56.1 (9.7)	6.5 (7.6); (0.2, 12.8), p=0.046	-0.6 (5.8); (-13.1, 12.0), p=0.926
Picture vocab	Exenatide	49.4 (9.1)	48.7 (11.5)	-0.7 (5.1); (-5.4, 4.0), p=0.722	
	Placebo	46.4 (11.9)	50.3 (12.5)	3.9 (7.0); (-2.0, 9.7), p= 0.161	-1.5 (6.2); (-15.0, 12.0), p=0.810
Oral reading	Exenatide	56.6 (11.6)	61.6 (14.3)	5.0 (11.9); (-6.0, 16.1), p=0.311	
	Placebo	53.3 (16.6)	60.6 (14.2)	7.4 (14.2); (-4.5, 19.3), p=0.186	0.9 (7.4); (-15.0, 16.9), p=0.900
Cognition Fluid					

Composite	Exenatide	38.4 (8.2)	52.9 (6.6)	14.4 (5.6); (9.3, 19.6), p=0.0005	
	Placebo	36.1 (11.6)	48.3 (12.7)	12.1 (4.5); (8.4, 15.9), p=0.0001	4.6 (5.4), (-7.0, 16.2), p= 0.406
Flanker	Exenatide	32.9 (5.2	38.1 (9.8)	5.3 (7.5); (-1.7, 12.3), p=0.113	
	Placebo	34.9 (8.7)	38.5 (10.8)	3.6 (8.5); (-3.5, 10.7), p=0.266	-0.4 (5.3), (-11.9, 11.2), p=0.945
Dimension change	Exenatide	36.0 (16)	45.0 (12.0)	9.0 (18.9); (-8.5, 26.5), p=0.254	
	Placebo	39.9 (13.1)	46.4 (15.4)	6.5 (7.1); (0.6, 12.5), p=0.036	-1.4 (7.2); (-17.0, 14.2), p=0.852
Pattern Comparison	Exenatide	44.7 (9.8)	58.3 (10.4)	13.6 (8.6); (5.6, 21.5), p=0.006	
	Placebo	46.6 (12.4)	59.4 (9.7)	12.8 (6.7); (7.2, 18.3), p=0.001	-1.1 (5.2); (-12.3, 10.1), p=0.837
List sort	Exenatide	49.1 (12.3)	56.1 (9.2)	7.0 (10.0); (-2.3, 16.3), p=0.114	
	Placebo	39.4 (10.4)	49.9 (9.6)	10.5 (6.2); (5.3, 15.7), p=0.002	6.2 (4.9); (-4.3, 16.8), p=0.221
Picture sequence	Exenatide	49.4 (5.3)	62.1 (13.2)	12.7 (12.1); (1.57, 23.9), p=0.032	
	Placebo	44.4 (7.4)	50.9 (15.2)	6.5 (13.7); (-5.0, 18.0), p=0.223	11.2 (7.4); (-4.7, 27.3), p=0.152

IIH Pressure cognitive scores. SD indicates standard deviation, SE, standard error; CI, confidence intervals.

FIGURE 24 - EXENATIDE EFFECT ON COGNITIVE SCORES



Exenatide effect on cognitive scores*. Cognitive testing was performed for all participants at week 0 before drug administration and at week 12. Graphs show mean change (SD) of fully corrected T-Scores for each cognitive domain and crystalised and fluid composite scores.*

5.5.3.2. IIH Pressure Med study cognition

There was no significant effect of any drug on the crystal composite, picture vocab or oral reading recognition scores. There was a significant reduction in the fluid composite score associated with acetazolamide (mean T-score (SE)), -5.00 (2.6), p=0.057 and topiramate -4.14 (2.0), p=0.061. Within the fluid domain there were significant reductions in performance seen in the dimension change test

with acetazolamide -10.3 (3.2), p=0.002, spironolactone -6.2 (2.8), p=0.03 and topiramate -7.0 (2.7) p=0.012. Topiramate also caused a significant reduction in the pattern comparison score, -6.3 (2.9), p=0.037. There were no significant effects in the fluid domain for amiloride or furosemide. (Table 28, Figure 25)

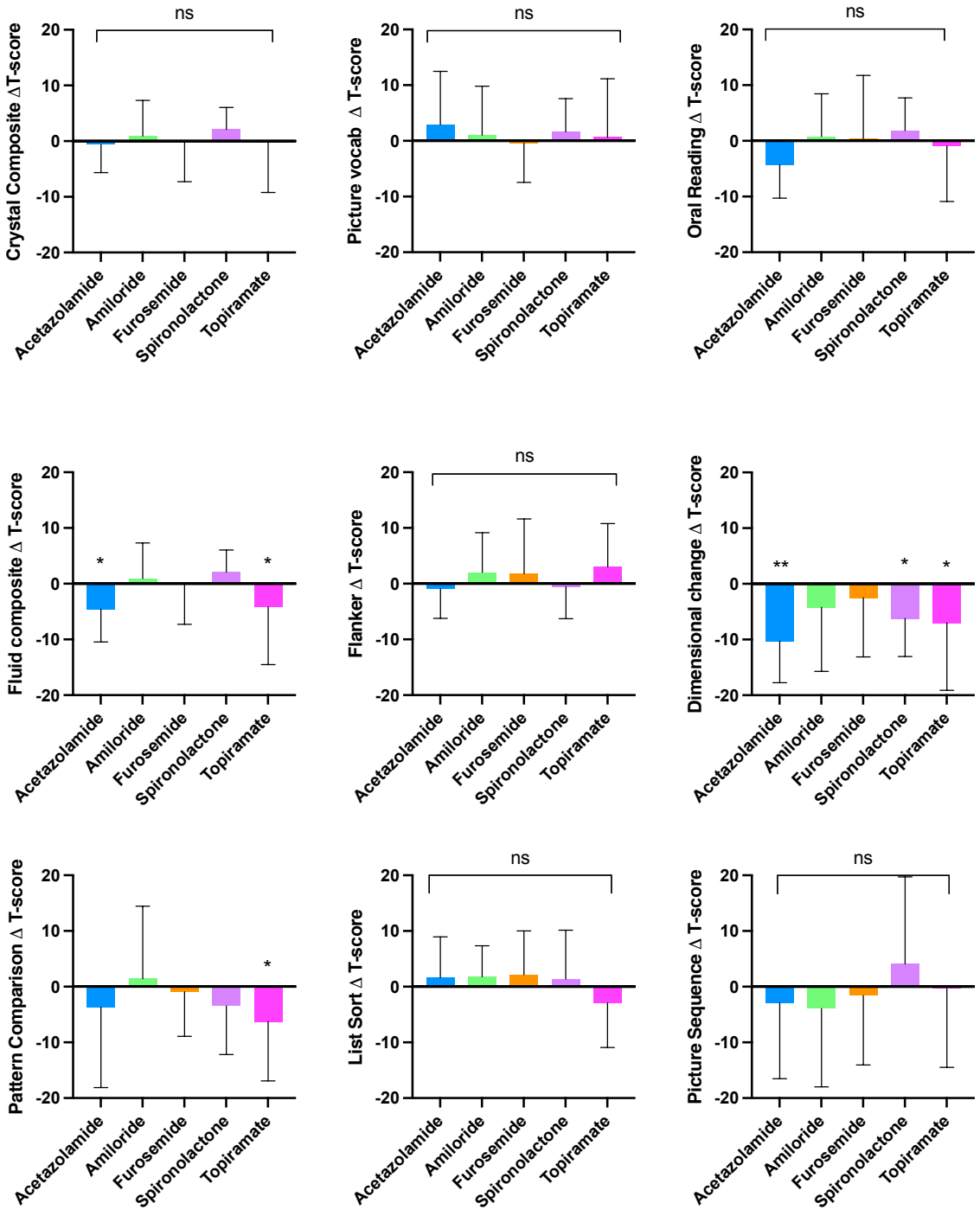
TABLE 28 - COGNITIVE SCORES IIH PRESSURE MED

Test	Treatment	T-score change mean (SE)	p=
Crystal composite			
	Acetazolamide	-0.6 (2.1)	0.777
	Amiloride	0.9 (1.8)	0.605
	Furosemide	-0.1 (1.8)	0.968
	Spironolactone	2.1 (1.9)	0.267
	Topiramate	-0.2 (1.8)	0.905
Picture vocab			
	Acetazolamide	2.9 (2.7)	0.286
	Amiloride	1.0 (2.3)	0.662
	Furosemide	-0.4 (2.3)	0.851
	Spironolactone	1.6 (2.4)	0.496
	Topiramate	0.6 (2.3)	0.778
Oral reading			
	Acetazolamide	-4.3 (2.7)	0.120
	Amiloride	0.8 (2.3)	0.734
	Furosemide	0.4 (2.3)	0.853
	Spironolactone	1.9 (2.4)	0.443
	Topiramate	-0.9 (2.3)	0.688
Fluid composite			
	Acetazolamide	-5.0 (2.6)	0.057*
	Amiloride	-0.9 (2.2)	0.695
	Furosemide	-0.3 (2.2)	0.896
	Spironolactone	-1.4 (2.3)	0.542
	Topiramate	-4.1 (2.2)	0.061*
Flanker			
	Acetazolamide	-1.4 (2.4)	0.557
	Amiloride	2.0 (2.0)	0.328
	Furosemide	1.8 (2.0)	0.382

	Spironolactone	-0.5 (2.1)	0.802
	Topiramate	3.0 (2.0)	0.145
Dimension change			
	Acetazolamide	-10.3 (3.2)	0.002**
	Amiloride	-4.2 (2.7)	0.125
	Furosemide	-2.5 (2.7)	0.359
	Spironolactone	-6.2 (2.8)	0.030
	Topiramate	-7.0 (2.7)	0.012*
Pattern comparison			
	Acetazolamide	-3.8 (3.5)	0.280
	Amiloride	1.4 (2.9)	0.630
	Furosemide	-0.9 (2.9)	0.754
	Spironolactone	-3.4 (3.1)	0.265
	Topiramate	-6.3 (2.9)	0.037*
List sort			
	Acetazolamide	1.6 (2.4)	0.507
	Amiloride	1.8 (2.0)	0.381
	Furosemide	2.1 (2.0)	0.294
	Spironolactone	1.4 (2.1)	0.512
	Topiramate	-2.9 (2.0)	0.153
Picture sequence			
	Acetazolamide	-2.9 (4.4)	0.516
	Amiloride	-3.9 (3.7)	0.299
	Furosemide	-1.6 (3.7)	0.677
	Spironolactone	4.1 (3.9)	0.299
	Topiramate	-0.4 (3.7)	0.924

*IIH Pressure Med cognitive scores. SE, standard error; * indicates p=<0.1; ** indicates p=<0.01.*

FIGURE 25 - DRUG EFFECT ON COGNITIVE SCORES



***Drug effect on cognitive scores**. Cognitive testing was performed for all participants at week 0 before drug administration and at week 2. Graphs show mean change (SD) of fully corrected T-Scores for each cognitive domain and crystalised and fluid composite scores.*

5.5.4. Cognition and headache

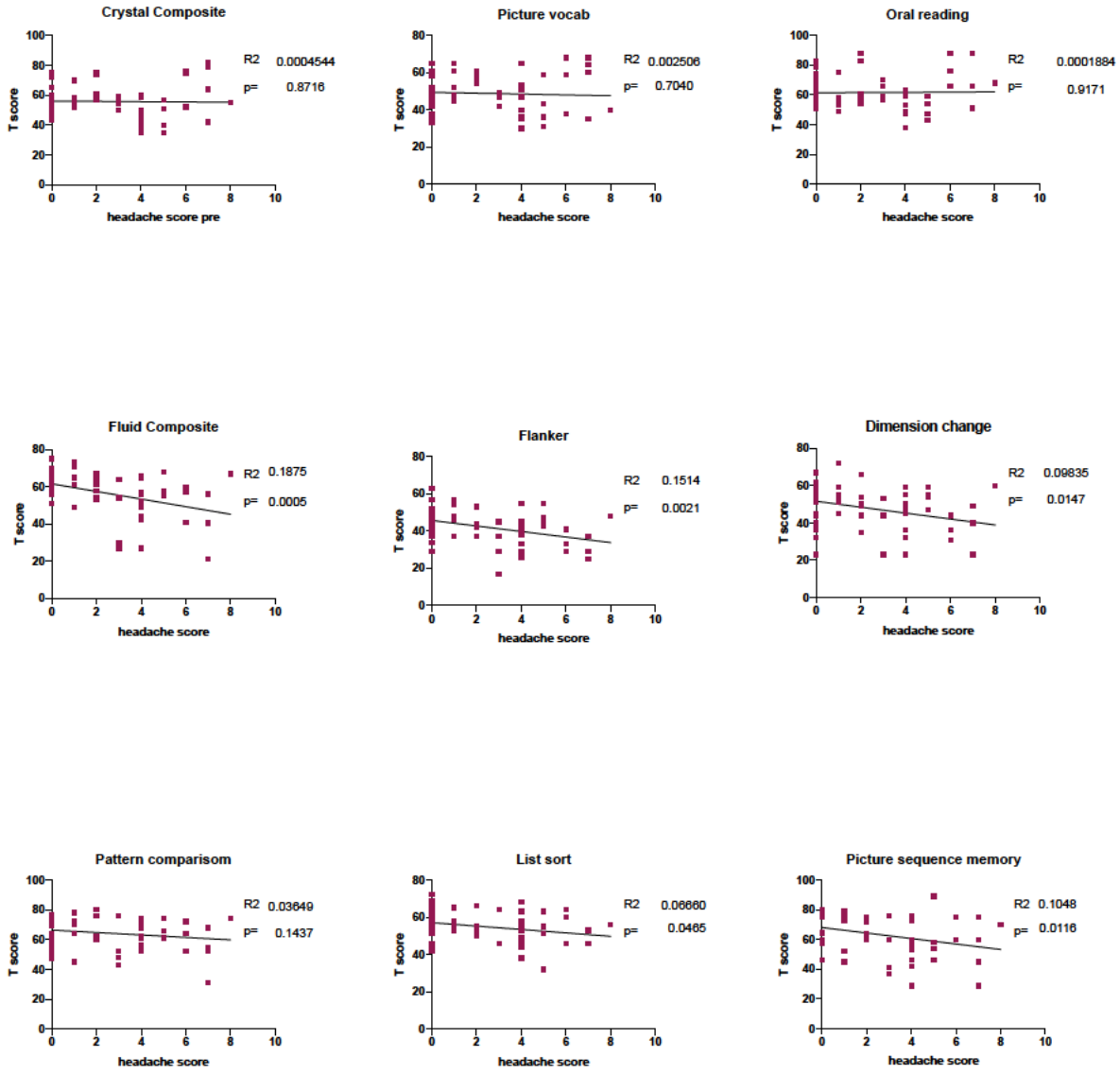
The effect of headache on performance of cognitive testing during baseline examinations was assessed. There was no relationship between headache and performance of crystalised cognitive scores. Significant correlations between increasing headache severity at the time of testing and worsening cognitive performance were found in most fluid domains, Flanker R^2 0.151, p=0.0021, Dimension change R^2 0.098, p=0.0147, List sort working memory R^2 0.067, p=0.047, Picture sequence memory R^2 0.105, p=0.012. A non-significant relationship was seen with Pattern comparison R^2 0.0365, p=0.14. (Table 29, Figure 26)

TABLE 29 - HEADACHE AND COGNITIVE PERFORMANCE CORRELATION

Test	R^2	p=
Crystal composite	0.0005	0.8716
Picture vocab	0.0025	0.7041
Oral reading recognition	0.0002	0.9171
Fluid composite	0.188	0.0005***
Flanker	0.151	0.0021**
Dimension change	0.0984	0.0147*
Pattern comparison	0.0365	0.1437
List sort	0.0666	0.0465*
Picture sequence	0.1048	0.0116*

*IIH Pressure Med headache and cognitive performance correlation. * Indicates p=<0.1; ** indicates p=<0.01, *** indicates p=<0.001.*

FIGURE 26 - RELATIONSHIP BETWEEN HEADACHE SEVERITY AND COGNITIVE PERFORMANCE



Relationship between headache severity and cognitive performance. *Headache severity was recorded during baseline cognitive assessment. Graphs show headache severity score (0-10 VRS) and cognitive performance (fully corrected T-score).*

5.6. Discussion

I report the first randomised sequential study to have investigated the effects of drugs on cognitive performance in IIH. I have shown that cognition can be negatively impacted by acetazolamide and topiramate, 2 commonly used treatments IIH. In addition, I have confirmed previous findings of impaired cognitive performance in IIH. I have identified that headache, one of the commonest symptoms of IIH, significantly impacts upon cognitive performance.

IIH is a chronic, relapsing disease characterised by raised ICP. There are a number of common disease manifestations including headache, papilloedema and visual disturbance. Patients also report cognitive fogging, this has been assessed in several small studies. To date only a single study has investigated the efficacy of a therapeutic intervention on cognitive performance in IIH.[57] The IIH Weight Trial (IIHWT) was a randomised controlled trial of bariatric surgery vs community weight loss in a cohort of women with IIH. An obese control group without IIH allowed baseline comparison between IIH and obesity. *Grech et al.*[117] demonstrated impaired executive function, using a bespoke battery of cognitive tests, in IIH compared to controls. They also demonstrated reversibility of cognitive impairment with decreased intra-cranial pressure. In that study cognition was also influenced by headache severity, depression and sleep apnoea.

In this study cognitive performance of the participants was evaluated with the standardised NIH Toolbox Cognition battery and expressed using fully corrected T-scores, corrected for age, sex, education and ethnicity.[163] The summary scores describe crystalised and fluid components of cognition in line with the 2 component theory of intellectual development.[164] In this paradigm crystalised abilities are related to knowledge and experience whereas fluid abilities reflect a person's

capacity to process and integrate information, solve novel problems and is related to general intelligence. Participants demonstrated normal cognitive ability in the crystalised domains. However cognitive performance in the fluid domain was more than 1 standard deviation below expected, fully corrected T-Score (mean (SE)) 37.2 (2.55). Within the fluid domain performance was particularly reduced in the Flanker 33.9 (1.85) and dimension change paradigms 38.1 (3.77) which reflect attention and executive function. The remaining fluid domains were reduced but not below 1 standard deviation. And reflect impaired processing speed and working memory. A reduction of 1SD on cognitive testing is thought to be clinically significant.[165]

The effects of drug treatment on cognition in IIH have not previously been assessed. Acetazolamide is the commonest drug treatment for IIH. Cognitive impairment is reported in patients taking this drug when it has been assessed in the setting of acute mountain sickness. Wang et al. demonstrated that despite improvements in acute mountain sickness volunteers administered acetazolamide had impaired attention, processing speed, reaction time, short-term memory, and working memory after rapid ascent compared to placebo.[118]

Topiramate is increasingly used for the treatment of IIH. Topiramate has class 1 evidence as prophylaxis in the treatment of migraine.[66-68] It also has well documented effects on weight loss.[69, 70] With the beneficial effect of weight loss in IIH[56] and headache one of the leading causes of morbidity in IIH, topiramate is of particular interest as a potential therapy. A 2007 trial reported by Celebisoy et al. randomised 40 patients with IIH to treatment with topiramate or acetazolamide, they found significant improvements in visual fields in both groups and no significant difference in treatment efficacy between the groups.[71] However topiramate commonly causes

cognitive impairment with deficits in many domains including verbal fluency, executive function and working memory.[119, 120]

In this study there was no significant effect of any drug on crystalised cognitive scores. There was a significant reduction in the fluid composite score associated with acetazolamide (mean T-score (SE)), -5.00 (2.6), p=0.057 and topiramate -4.14 (2.0), p=0.061. Within the fluid domain there were significant reductions in performance seen in the dimension change test with acetazolamide -10.3 (3.2), p=0.002 and topiramate -7.0 (2.7) p=0.012. Topiramate also caused a significant reduction in the pattern comparison score, -6.3 (2.9), p=0.037. There was no significant change in cognition with exenatide, amiloride, furosemide and spironolactone administration. These scores demonstrate effects of acetazolamide and topiramate on executive function and processing speed and are attested to by reported cognitive effects in both drugs by participants. However cognitive side-effects where more commonly reported by participants with topiramate which might in part reflect a nocebo effect due to inclusion of cognitive side-effects in the patient information given during the study.

Headache has been shown to affect cognitive performance with several studies confirming impairment during migraine attacks.[121-125] The IIHWT reported deficits in attention correlated with headache severity in IIH patients.[117]

This study has confirmed these findings and additionally shows reduced performance across several cognitive domains correlated with headache severity during testing. There was no relationship between headache and performance of crystalised cognitive scores. However, significant correlations

between increasing headache severity and worsening cognitive performance were found in most fluid cognitive domains, Flanker R^2 0.151, p=0.0021, Dimension change R^2 0.098, p=0.0147, List sort working memory R^2 0.067, p=0.047, Picture sequence memory R^2 0.105, p=0.012. These relationships demonstrate effects on attention, executive function and working memory.

There are several limitations to this study. The study did not recruit a separate control group, however cognitive comparisons are made to the NIH Toolbox Cognition Battery normative population (n=1038),[163] although this is validated in the United States as opposed to the UK. Although educational and cultural effects would be expected to be seen in the crystalised scores as opposed to fluid cognitive domains whilst the converse was found in this study. As an exploratory study it was not powered to detect drug effects on cognition. Furthermore the protocol did not account for learning effects in early iterations of testing which may have diluted any observable effect in the assessment of exenatide, although the study was randomised and the learning effect would be less pronounced in the later Pressure Med study.

It can be hypothesised that reduced cognitive performance in IIH is a result of the raised ICP state impairing normal CSF and in turn glymphatic function. Given the demonstrated efficacy of acetazolamide and topiramate to reduce CSF pressure that effect must be outweighed by the deleterious side-effects of those drugs on cognition, independent of the ICP lowering effect. In spite of the lack of effect seen with exenatide and other agents a clear advantage would be suggested over existing treatment with even a neutral effect on cognition.

The results of this study have implications for future study design and informing treatment guidelines. Cognitive symptoms and impairment are significant in patients with IIH and are worsened by treatment with 2 commonly used drug treatments, acetazolamide and topiramate. Whilst exenatide, amiloride, furosemide and spironolactone did not have a deleterious effect on cognitive performance. Given the importance and prevalence of cognitive symptoms in patients with IIH it would seem necessary for cognitive symptom reporting and psychometric testing to be included in future later phase interventional studies that will inform future clinical management.

5.7. Conclusion

This study demonstrates that cognitive impairment is present in IIH and can be quantified using a rapid standardised test (NIHTB-CB).

Cognitive dysfunction is further impaired when patients utilise drug therapy with acetazolamide and topiramate. This is likely to be clinically relevant as patients also described cognitive side-effects.

These results have important clinical implications when weighing up the pros and cons of prescribing in IIH and consideration should be made for the inclusion of psychometric testing in future later phase interventional studies.

6. Summary and future directions

Over the course of this thesis, I have reported findings from the IIH Pressure and Pressure Med studies highlighting novel aspects of ICP Physiology in IIH, the effect of exenatide on ICP and the effects of other drugs commonly used to treat IIH on ICP. I went on to report the effects of those drugs and headache on cognition.

In chapter 2 the physiology study demonstrated that ICP does not appear to have a diurnal variation in IIH, but varies by position and duration in that position. ICP rose at night whilst the patient was continuously supine. This knowledge gives reassurance that ICP can be accurately measured and compared at any time of day and can inform future clinical study.

IIH Pressure demonstrated that Exenatide reduced ICP acutely and after chronic dosing and improvements in headache and visual function were recorded. GLP-1R agonists represent a new approach to treat IIH.

The IIH Pressure Med Study assessed Acetazolamide, furosemide, spironolactone and topiramate; all reduced ICP significantly, but there was no statistical difference between any treatment. Cognitive side-effects were common with acetazolamide and topiramate and detailed cognitive assessment demonstrated significantly worse performance following treatment.

Future physiology work will be directed at investigating the relationship between ICP and headache and ICP changes with exercise. The IIH pressure study has provided confidence to proceed to a phase

3 trial of GLP-1 agonists in IIH in the near future, it also highlights the potential to utilise GLP-1 agonists in other conditions of raised ICP including traumatic brain injury. The findings of these studies and potential future phase 3 study will help to change clinical practice in the management of raised ICP conditions in the future.

7. References

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8. IIH Pressure protocol

TRIAL PROTOCOL

IIH Pressure

The acute and chronic effects of gut neuropeptides on intracranial pressure regulation

Sponsor reference number	RG_16-122
ISRCTN number	
REC reference number	17/WM/0179

Protocol development and sign off

Protocol Contributors	
The following people have contributed to the writing of this protocol:	
Name:	Affiliation and role:
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Dr James Mitchell	Investigator
Miss Susan Mollan	Investigator

Protocol Amendments				
The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version				
Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
1	26/May/2017	1.1	REC provisional opinion and HRA review	Changes as requested by REC and HRA
2	15/09/2017	1.3	Non-substantial	Sentences added to clarify aims of part 2 study

PI Signature Page	
This protocol has been approved by:	
Trial Name:	The acute and chronic effects of gut neuropeptides on intracranial pressure regulation
Protocol Version Number:	Version: 1.3
Protocol Version Date:	15 / Sep / 2017
PI Name:	Dr Alex Sinclair
Trial Role:	Principal Investigator
Signature and date:	_____ __ __/__ __/__ __ __ __
Sponsor statement:	
Where the University of Birmingham takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.	

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8.1. TRIAL SUMMARY

8.1.1. Title

IIH Pressure: The acute and chronic effects of gut neuropeptides on intracranial pressure regulation

8.1.2. Trial Design

The trial is a prospective, randomised, placebo controlled, parallel group, explorative trial. The active treatment group will be treated with Exenatide and the control group with placebo. In the second (optional) part of the trial the treatment group will be treated with existing drugs used to treat IIH, namely acetazolamide, spironolactone, furosemide, amiloride and topiramate.

8.1.3. Objectives

8.1.3.1. Primary Aims

- The trial will assess the biological role of acute administration of Exenatide on intracerebral pressure (ICP).
- The trial will assess the biological role of chronic administration of Exenatide on ICP.

8.1.3.2. Secondary Aims

- Evaluate the acute and chronic effects on the biological role of Exenatide on Central Nervous System (CNS) and systemic adipokines, inflammatory cytokines, biomarkers, headache and quality of life.

8.1.4. Participant Population and Sample Size

The trial will be conducted in a population of women diagnosed with active Idiopathic Intracranial Hypertension (IIH). Sample size will be 8 participants per arm – a total of 16 participants.

8.1.5. Primary Endpoints

- Change in ICP between baseline and 24hrs post drug administration
- Change in ICP between baseline and end of trial visit
- Change in ICP baseline vs 2.5 hours post administration

8.1.6. Secondary Endpoints

The trial will evaluate the biological effects of exenatide on modulation of serum and Cerebrospinal fluid (CSF) adipokines, gut neuropeptides, biomarkers, fat distribution, serum and CSF Exenatide levels, headache measures and quality of life (QoL) measures after acute and chronic administration.

8.1.7. Exploratory Endpoints

To assess acute responses of ICP to drugs commonly used in IIH (acetazolamide, spironolactone, furosemide, amiloride and topiramate), and the change in ICP between Exenatide and the other drugs used to reduce intra-cerebral pressure at 2 weeks. The Trial does not aim to establish clinical efficacy.

8.1.8. Sub-study aims

OCT

To evaluate biofluid biomarkers, including Optical Coherence Tomography (OCT) biomarkers to monitor ICP.

Sleep Apnoea

To assess the relationship between sleep and overnight ICP recording in an IIH population.

Intra-ocular Pressure

To evaluate the response of intra-ocular pressure to the administration of Exenatide and the relationship between ICP and Intra-ocular Pressure (IOP).

ICP variability

To assess the normal variability of ICP in an IIH population acutely over 24-hours and intermittently over a 3-month observation period.

Headache

To assess the relationship between headache, ICP and Exenatide.

8.1.9. Key Eligibility Criteria

Female

Active IIH as diagnosed by the modified Dandy criteria

Not treated with GLP-1 agonist or DPP-4 inhibitor

No functioning CSF shunting procedure (patients with previous failed shunts can be included)

8.1.10. Intervention

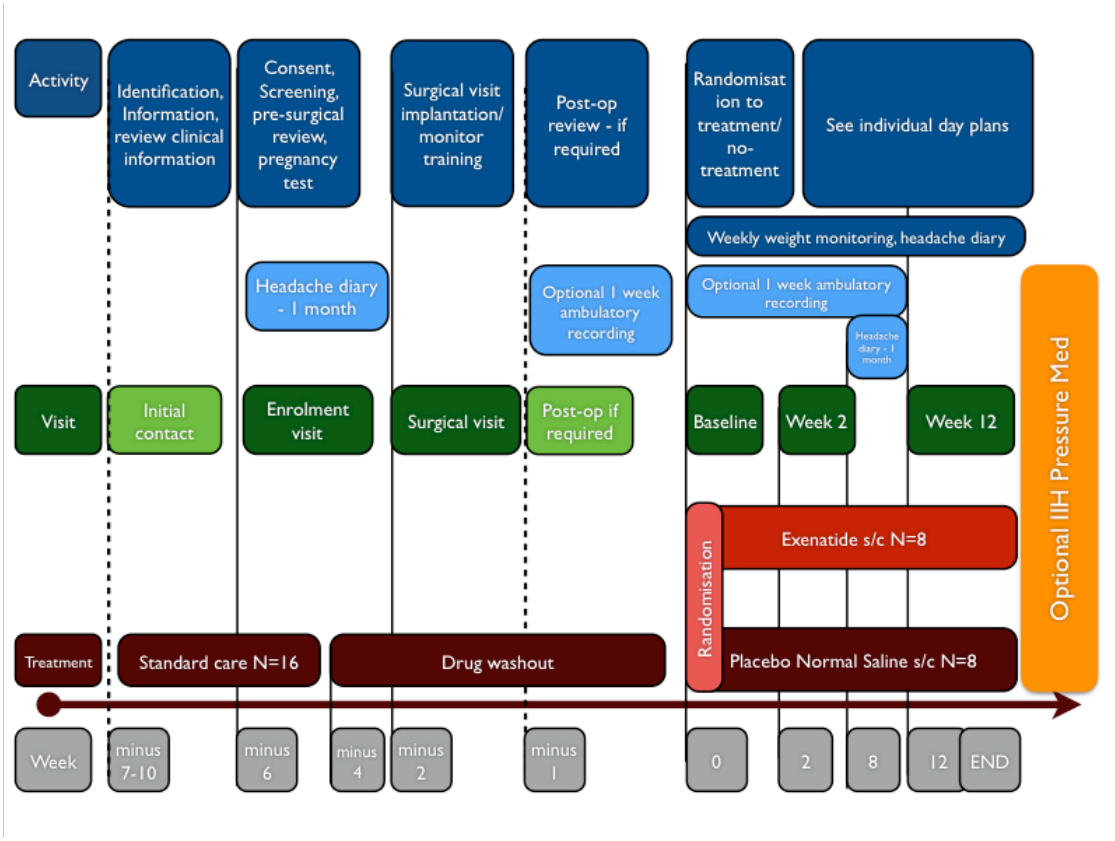
Participants in the active arm will be treated with the GLP-1 agonist drug Exenatide. Initial dose will be a single bolus of 20mg s/c at visit 1. The control arm will receive normal saline s/c placebo for the first 24 hours. For the 3-month continuation study phase patients will be dosed with Exenatide 10mg BD s/c and the control group will receive normal saline placebo s/c. In the second (optional) part of the trial all participants will be treated with the five study medications in random sequence. They will have one week of titration, followed by one week at a treatment dosage and then the drug will be discontinued. There will be a washout period between each round. The drug dosages are as follows:

- Acetazolamide: Patients will take 500mg BD PO immediate release for 7 days, followed by 1g BD for 7 days.
- Spironolactone: Participants will take 100mg OD PO for 7 days, followed by 200mg OD for 7 days.
- Amiloride: Participants will take 10mg OD PO for 14 days.
- Furosemide: Patients will take 40mg OD PO for 7 days, followed by 80mg OD for 7 days.

- Topiramate: Participants will take 25mg BD PO for 4 days, followed by 25mg mane/50mg nocte for 3 days followed by 50mg BD for 7 days.

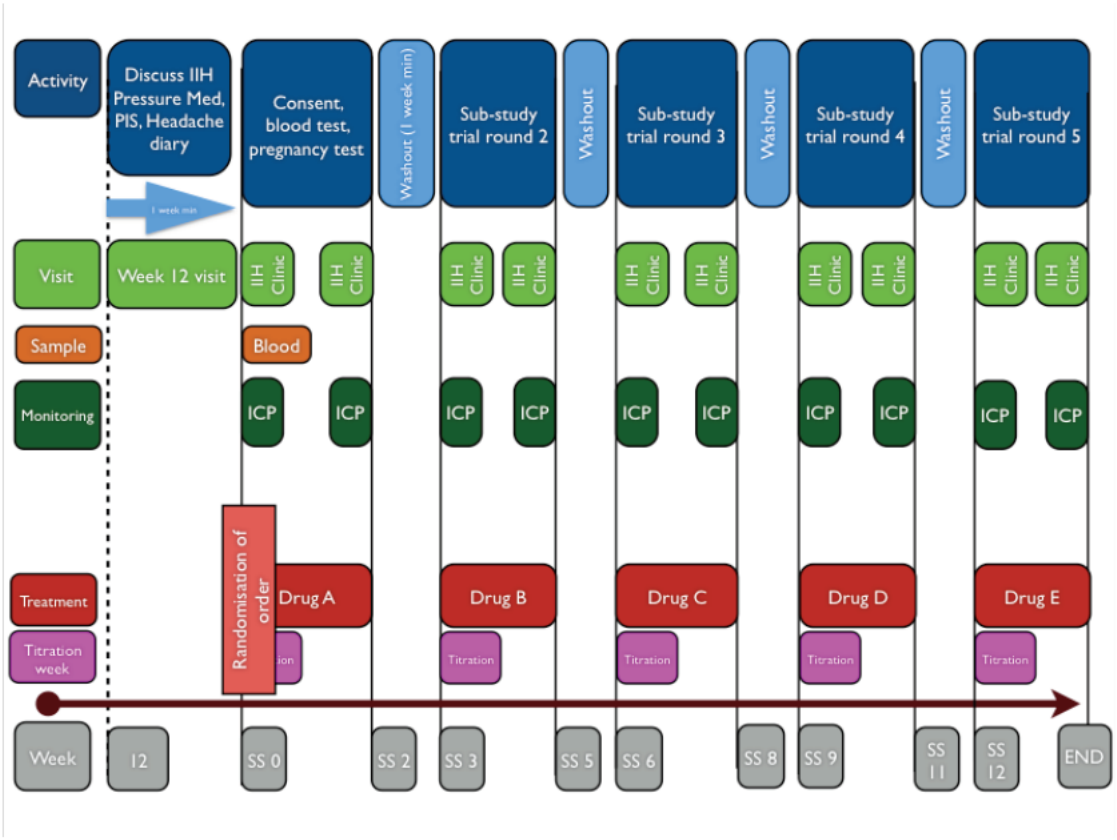
8.1.11. Trial Schema

FIGURE 27 - TRIAL SCHEMA



8.1.12. IIH Pressure Med Schema

FIGURE 28 - IIH PRESSURE MED SCHEMA



8.2. Background and Rationale

Gut neuropeptides are increasingly being recognised for their role in the central nervous system (CNS). A principal gut neuropeptide is glucagon like peptide 1 (GLP-1) predominantly secreted from the distal small intestine in response to a meal. GLP-1 is principally known to stimulate insulin release, proliferation of pancreatic beta cells and reduces blood glucose in diabetics.[82]

Within the brain, GLP-1 signals centrally mainly through GLP-1Receptor (GLP-1R), a G-coupled protein receptor expressed in selected cell types within the pituitary gland, hypothalamus, hippocampus, olfactory cortex, circumventricular organs and interestingly the choroid plexus.[85] GLP-1 crosses the blood brain barrier,[86] and can be detected in the cerebrospinal fluid.[87] However, the pathways by which gut secreted GLP-1 exerts central effects are debated: 1) binding to vagal afferents, or 2) via the blood brain barrier.[88] The vagus nerve can also stimulate GLP-1 production at the nucleus tractus solitarius with a dense and widespread network of GLP-1 fibres reaching the ventricles and CSF.[83]

In additional to the role in regulating glycaemia GLP-1 has been shown to have actions in the CNS. GLP-1 is involved in regulating satiety and weight through signalling at the hypothalamus.[84] Interestingly, meal stimulated levels of GLP-1 are lower in obese patients.[90] GLP-1 agonists are used therapeutically to promote weight loss.[84] GLP-1 has also been shown to have anti-inflammatory effects and potentially neuroprotective properties in *in-vitro* and *in-vivo* models of Parkinson's and Alzheimer's disease.[91]

There is also growing evidence that GLP-1 may have a role in fluid secretion. In the renal proximal tubule GLP-1 acts to reduce sodium resorption and promote diuresis.[92, 93]

The choroid plexus is the fluid secreting structure within the brain producing the majority of the cerebral spinal fluid (CSF). The structure of the choroid plexus epithelial cells is analogous to an inverted renal proximal tubule with a similar mechanism of fluid secretion and hence GLP-1 may also reduce CSF secretion in the brain.

We have explored the impact of gut neuropeptides in vitro and in vivo. Preliminary data suggests that at the choroid plexus contains GLP-1 receptors which are upregulate when activated by a GLP-1 agonist. Additionally in vitro assays of CSF secretion are inhibited by GLP-1 through a cAMP/protein kinase A dependent pathway. GLP-1 also regulates fluid dynamics and reduces intracranial pressure in the rodent. Whilst our early observations are robust, we do not yet know if the findings will translate to the clinical setting and to what extend GLP-1 mediates choroid plexus fluid regulation and intracranial pressure. Additionally, the effects of GLP-1 on CNS inflammation and adipokines profiles are not determined in humans.

In this study we aim to evaluate the effects of GLP-1 agonists on CNS fluid secretion in humans. We will study the effects of the GLP-1 analogue, Exenatide, in patients with idiopathic intracranial hypertension (IIH). Patients with IIH are an ideal population in which to study the CNS effects of gut neuropeptides as patients are typically obese with evidence of central adipokine dysregulation.[100] Patients also have elevated ICP.[101] Effects of GLP-1 on fluid secretion at the choroid plexus are

reflected in alterations in ICP which can be evaluated though telemetric intracranial pressure monitoring.

Telemetric intracranial pressure monitors are increasingly being used clinically and for research.[18] They provide many advantages particularly allowing frequent and accurate monitoring of pressure; which is non-invasive following initial implantation. The telemetric probes are inserted surgically under local or general anaesthesia via a burr-hole with placement of the probe into the brain parenchyma of the right frontal lobe. The safety profile has been established.[19] The risks are minimal and relate to the surgical procedure itself; of note however is driving status. Currently patients need to desist from driving and inform the DVLA once a monitor is placed and request permission to resume driving, a process that can take some weeks. Rarely telemeters can fail in use, in this instance replacement would be necessary involving a further surgical procedure if the participant agreed.

There are several medications presently used for IIH, there is only some class one evidence of efficacy for acetazolamide[53] and minimal *in vitro*, *in vivo* or clinical evidence for other drugs in current use including topiramate, furosemide, amiloride and spironolactone. All of which are thought to principally reduce ICP through reduced CSF secretion. There are no studies available presently to guide the choice of these drugs in individual patients. We would like to offer the opportunity to test the current drugs used therapeutically whilst they have an ICP telemeter in place. This would provide some data about the effects of these medications on ICP at both an individual level and across a small group. It would also inform the clinical team of individual patient responses to commonly used drugs for this condition and guide future dedicated clinical trials.

8.2.1. Sub-studies

Optical Coherence Tomography

OCT is a sophisticated eye scanning technique which we will utilise in the main study to analyse the response of the eye to treatment and potential ICP lowering. The scanning technique is non-invasive and uses laser light to produce a wealth of data including thicknesses of the structures at the back of the eye including the retinal cell layers injured in IIH.

Sleep apnoea and ICP

Obstructive Sleep apnoea is a condition commonly encountered in patients with IIH and it is thought to have a relationship with variability of ICP overnight. We aim to investigate this by using a non-invasive sleep monitor during the study admission.

Intra-ocular pressure

The mechanism of aqueous secretion in the eye is similar to that of CSF secretion. We plan to measure the biological response to Exenatide of intra-ocular pressure, measured by tonometry, over the time course of the study and also the relationship between IOP and ICP changes.

Fat

Exenatide has been shown to induce changes in fat distribution in a diabetic population,[99] we aim to investigate fat distribution changes in response to Exenatide in an IIH population.

8.2.2. Optional sub-studies

ICP variability

ICP varies throughout the day in tandem with posture but might also vary due to a wide variety of other variables. This has not been studied in an IIH population before and the utilisation of indwelling continuous ICP monitoring will allow this for the first time. We will investigate the normal variation in ICP in the IIH population by monitoring ICP over a continuous period whilst patients undertake normal daily activities and also a short monitoring programme following changes in posture over 24 hours both before the baseline of the study and during the study period.

CSF

The CNS penetration of Exenatide may be investigated via optional CSF sampling and comparing the drug levels in the CSF and serum. This will be offered to patients as an option. This would be completed by insertion of a lumbar catheter allowing multiple CSF sampling with matched serum samples. Lumbar catheter insertion is a common neuro-surgical procedure which carries the same risk profile as lumbar puncture when in place for short (24hour) time periods. To prevent sampling altering ICP measures the small volumes of CSF removed will be replaced with sterile saline (as occurs in a clinical infusion study).

Headache

Headache will be assessed in depth in the main study. Calcitonin Gene-Related Peptide (CGRP) is a peptide whose importance in the pathogenesis of headache in increasingly appreciated and has a role as a headache biomarker and treatment target. CGRP varies with headache presence (higher during severe headaches); CGRP levels cannot be meaningfully measured in peripheral blood samples but can be in jugular venous samples. Jugular venous sampling is safely undertaken in normal clinical settings and as a part of other procedures, we would aim to take small samples of venous blood under ultrasound guidance at the initial (surgical or baseline visits) and final visit, or another occasion where patients were willing, aiming to take 2 samples – one where a severe headache was present and one without. This will be offered to all patients as an optional study.

8.3. Aims, Objectives and Endpoints

8.3.1. Hypothesis

Exenatide modulates fluid secretion and inflammatory biomarkers in the central nervous system following acute administration.

8.3.2. Primary Aims

- The trial will assess the biological role of acute administration of Exenatide on ICP.
- The trial will assess the biological role of chronic administration of Exenatide on ICP.

8.3.3. Secondary Aims

- Evaluate the acute and chronic effects on the biological role of Exenatide on CNS and systemic adipokines, inflammatory cytokines, biomarkers, headache and quality of life.

8.3.4. Primary Endpoints

- Change in ICP between baseline and 24hrs post drug administration
- Change in ICP between baseline and end of trial visit
- Change in ICP baseline vs 2.5 hours post administration

8.3.5. Secondary Endpoints

The trial will evaluate the biological effects of exenatide on modulation of serum and CSF adipokines, gut neuropeptides, biomarkers, fat distribution, serum and CSF Exenatide levels, headache measures and QoL measures after acute and chronic administration.

8.3.6. Exploratory Endpoints

To assess acute responses of ICP to drugs commonly used in the treatment of IIH, and the change in ICP between Exenatide and other drugs used to reduce intra-cerebral pressure at 2 weeks.

- The trial does not aim to establish clinical efficacy.

8.3.7. Sub-study aims

OCT

To evaluate biofluid biomarkers, including OCT biomarkers to monitor ICP.

Sleep Apnoea

To assess the relationship between sleep and overnight ICP recording in an IIH population.

Intra-ocular Pressure

To evaluate the response of intra-ocular pressure to the administration of Exenatide and the relationship between ICP and IOP.

ICP variability

To assess the normal variability of ICP in an IIH population acutely over 24 hours and intermittently over a *3-month* observation period.

Headache

To assess the relationship between headache, ICP and Exenatide.

8.4. Trial Design and Setting

8.4.1. Trial Design

This trial is designed to examine the effects of a GLP-1 agonist upon CSF regulation and CNS biomarkers following acute and chronic administration of Exenatide. The second part of the trial is designed to examine the effects of 5 existing drug treatments of IIH on ICP acutely and at 2 weeks and to compare those effects with that of exenatide.

This is a prospective, randomised, parallel group, placebo controlled, exploratory trial in 16 female patients with idiopathic intracranial hypertension. 16 patients with a diagnosis of IIH will be identified and recruited. Participants will have a telemetric ICP monitor implanted. In the first part participants will be randomised to Exenatide or a control group; allocation is 1:1. In the second part all patients will take five drugs commonly used for IIH in sequence for a total of 2-weeks each with a washout period between. Order will be randomised.

Patients on drugs such as acetazolamide or other ICP manipulating drugs will need to discontinue these for 1-month prior to enrolment.

Following enrolment, there will be a 1-month run-in period prior to implantation of the ICP monitor to allow the recording of a headache diary (headache days, migraine days, headache severity 0-10 VRS, days of analgesic use) (appendix G).

Surgical implantation of ICP monitor may be conducted under local or general anaesthesia – decision making will be by the surgical team in consultation with the participant. Implantation can occur immediately prior to baseline if agreed with the participant. Rarely telemeters can fail in use. If this were to occur, we would offer to replace with a new monitor, requiring a further surgical procedure, if the participant agreed.

Patients will attend baseline fasted, regulated meals will be provided subsequently, this is detailed in section 2.8 below. At the baseline visit patients will be randomised to either Exenatide or a control arm. Initially a Dual-energy X-ray absorptiometry (DEXA) scan (fat distribution), visual testing, IOP, headache scores and questionnaires will be conducted; as detailed in section 2.8 below. Then continuous telemetric ICP monitoring will commence. Sleep monitoring will occur overnight.

Following a 1-hour baseline recording of ICP participants will receive active treatment with subcutaneous dosing of 20mg of Exenatide or placebo treatment with a subcutaneous saline injection. Continuous ICP monitoring will continue for 24hours post first dose. A second dose will be administered on day 2 (10mg Exenatide or saline placebo and ICP monitored for a further 3 hours). Treatment allocation will be blinded to patient and investigators. Serum samples will be collected at time points as at section 8 and sampling protocol (appendix F).

CSF sampling may be undertaken in patients as an optional procedure – the rationale and procedure is explained below. Following the baseline visit the groups will proceed for a further 3-months receiving either twice daily Exenatide 10mg or placebo as per initial randomisation. During the 3-month phase both groups will monitor body weight weekly with supplied scales.

Participants will return for a brief visit at 2 weeks to record ICP over a 1-hour period, if this coincides with home monitoring this visit could be obviated.

At the end of the 3-month phase patients will attend for the 12-week visit. Patients will attend fasted from midnight. This visit will consist of a DEXA scan, visual testing, IOP, questionnaires, headache scoring and blood sampling. Then continuous telemetric ICP monitoring will commence for 3 hours. Procedures are detailed in section 2.8.

Participants will have the option of additional home intermittent ICP monitoring before and during the 3-month dosing phase.

In the study day we propose to give Exenatide as a single 20mg dose. Exenatide is safe at this dosing in the product literature, but side-effects of nausea can occur. Participants will be warned of this side-effect and anti-emesis can be given, if necessary, but it is usually a well-tolerated drug.

Randomisation will be conducted through a phone randomisation service in blocks as set out in section 2.6.2. An interim analysis will occur after the first block.

Participants will be given the option at the end of this part to continue with the IIH Pressure Med investigation. This is an open label, randomised, cross-over, exploratory study which will recruit all

willing participants of the main trial. The aim is to explore the acute effects of drugs used in routine clinical practice on intracranial pressure as measured by telemetry and at 2 weeks. Five drugs will be given to each participant in sequence with the order randomised. There will be a week of dose titration followed by a week of treatment dosing. There will be a minimum 1-week wash-out period between drug administrations.

The trial design has been submitted to and reviewed by the Medicines and Healthcare products Regulatory Agency (MHRA) who have confirmed that it does not constitute a Clinical Trial of an Investigational Medicinal Product (CTIMP).

- The trial does not aim to establish clinical efficacy.

8.4.2. Optional Sub-studies

ICP variability

The ICP variability of IIH patients will be investigated in this study by offering participants the option to take an ICP monitor home for a 1-week period prior to commencement of the trial and for a further week during the trial where they will record ICP over a set programme of posture changes over a 24-hour period and through the week (utilising UHB clinical proforma). This will give valuable data regarding the variability of ICP in this patient cohort.

CSF

Participants may be given the option of also providing CSF samples at intervals over the baseline visit via lumbar catheter. These samples will allow exploration of the movement of Exenatide through the blood-brain barrier (through comparison of CSF to serum levels).

Headache

All participants will be given the option to provide jugular venous blood samples for the measurement of CGRP. This will be undertaken at the surgical, or baseline visit, and at the week-12 visit, or other occasion at the participant's request. The aim is to take 1 sample during a severe headache and one sample at another time. These samples will allow the relationship between CGRP and headache scores to be assessed in an IIH cohort.

8.5. Trial Setting

Suitable patients will be identified at Neuro-ophthalmology clinics at University Hospitals Birmingham (UHB) NHS Trust (as well as at PIC sites section 6.1.1). Participants will be enrolled at UHB, the trial will be undertaken in the Clinical Research Facility (CRF) and Institute of Translational Medicine (ITM) at UHB.

8.6. Eligibility

8.6.1. Inclusion Criteria

1. Female IIH patients aged between 18 and 60 years, diagnosed according to the modified Dandy criteria who have active disease (papilloedema [Frisen grade ≥ 1], significantly raised ICP > 25cmH_2O) and no evidence of venous sinus thrombosis (magnetic resonance imaging (MRI) or computerised tomography (CT) imaging and venography as noted at diagnosis).
2. Able to give informed consent.

8.6.2. Exclusion Criteria

1. Age less than 18 or older than 60 years.
2. Pregnant or trying to conceive.
3. 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.
4. Addison's or Cushing's disease.
5. Functioning CSF shunt/stent or optic nerve sheath fenestration.
6. Currently using GLP-1 agonist or DPP-4 inhibitor.
7. Surgical contra-indication.
8. Concomitant therapy with acetazolamide, topiramate or diuretics (this can be discontinued 1 month prior to enrolment).
9. Inability to give informed consent e.g. due to cognitive impairment.

8.7. Consent

It will be the responsibility of the Investigators to obtain written informed consent for each participant prior to performing any trial related procedure. A Participant Information Sheet (PIS) will be provided to facilitate this process. Investigators will ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the participant. They will also stress that participation is voluntary and that the participant is free to refuse to take part and may withdraw from the trial at any time. The participant will be given a minimum of one week to read the PIS and to discuss their participation with others outside of the site research team. The participant will be given the opportunity to ask questions.

If the participant expresses an interest in participating in the trial, they will be asked to sign and date the latest version of the Informed Consent Form (ICF) (appendix B). "The participant must give explicit consent for the regulatory authorities, members of the research team and representatives of the sponsor to be given direct access to the participant's medical records".

The Investigator will then sign and date the form. A copy of the ICF will be given to the participant, a copy will be filed in the medical notes, and the original placed in the Investigator Site File (ISF). Once the participant is entered into the trial, the participant's unique trial identification number will be entered on the ICF maintained in the ISF.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS and date given to participant, and version number of ICF signed and date consent received.

Where consent is obtained on the same day that the trial related assessments are due to start, a note will be made in the medical notes as to what time the consent was obtained and what time the procedures started.

At each visit the participant's willingness to continue in the trial will be ascertained and documented in the medical notes. Throughout the trial the participant will have the opportunity to ask questions about the trial. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider and if happy to continue will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

Details of all participants approached about the trial will be recorded on the Participant Screening/Enrolment Log and with the participant's prior consent, their General Practitioner (GP) and usual treating specialist will also be informed that they are taking part in the trial (appendix I).

Participants will be asked at the end of the first part of the trial to enrol in the IIH Pressure Med investigation. Consent will be taken as per above and recorded on the IIH Pressure Med consent form (PMCF) (appendix D).

8.8. Enrolment and Randomisation

8.8.1. Enrolment/Registration

8.8.1.1. Identifying potential participants

Research staff at UHB will identify potential participants from the Neuro-ophthalmology clinic, which provides one of the largest IIH services in the country with a strong track record in IIH research. UHB hospital informatics will be used to generate queries allowing the clinical teams to identify potential participants with basic eligibility criteria (e.g. coded IIH on discharge). These patients will then be approached to establish any interest in taking part in the IIH Pressure trial.

Additionally, potential participants will be identified and referred to trial sites from Patient Identification Centre (PIC) sites. In these cases the patient details will be sent to the research team at the trial site who will then contact the potential participant. Participants will not be consented at PIC sites.

General IIH research flyers will also be available in appropriate clinics e.g. Neuro-ophthalmology and Neurology, and will be used to increase awareness of the research. The hospital newsletter and hospital and university social media may also be used for advertising purposes. An advertisement will also be posted on the research group's Facebook page and on the IIH:UK charity website (appendix E).

If patients subsequently indicate that they are interested in participating in general IIH research this will be documented in their patient notes, and these potential participants will be approached during their next outpatient clinic appointment or be referred by their treating physician.

8.8.1.2. Enrolment

Following identification an investigator will conduct either a telephone or face-to-face consultation (research clinic visit) to discuss the trial and assess eligibility. Potential participants who may be eligible will be offered full details of the trial and provided with a written PIS (appendix A) either in person or by post.

If they are interested, they will be invited to an enrolment visit. The details of the trial will be discussed in full and the participant's eligibility will be discussed. If they are happy to proceed and eligible they will be asked to give written consent (appendix B) to enrol in the full trial. The trial consent will include surgical consent as delegated to the investigators by the surgeon. Urine Human Chorionic Gonadotrophin (HCG) testing will be completed at enrolment and baseline visits.

On the day of surgery consent to the surgical procedure and to participate in the trial will be re-affirmed by the surgical team. Surgical consent will follow clinical norms.

Potential participants will have time between contact and the enrolment visit (at least a week) to consider the trial and decide whether or not they wish to take part, and to discuss the trial with their family and friends if they would like to do so. If the potential participant has any questions or queries about the trial during this time they will have the opportunity to discuss the study with the research staff, whose contact details will be provided on the PIS. It will be explained that if the potential

participant enrols but later decides not to take part in the trial this will not affect their continuing medical care.

We plan to promote retention by covering reasonable travel expenses for participants and by giving a small thank you payment of £100 at the end of the participants' involvement in the trial, where participants are withdrawn through no fault of their own a pro-rata payment will be made.

At the end of the first part of the trial all participants will be approached regarding enrolling in the "IIH Pressure Med" investigation. They will be provided with the IIH Pressure Med PIS (appendix C) and given an appointment to attend for commencement of this part of the trial. There is also information about the IIH Pressure Med investigation in the main PIS (appendix A). Patients will have a minimum of 1 week from the week 12 visit before commencing the IIH Pressure Med part of the trial.

8.8.1.3. Randomisation

For allocation of the participants, a computer-generated randomised list will be used. This will be generated by Birmingham Clinical Trials Unit (BCTU) and passed to an independent pharmacist. A double check of allocation will be performed by the unblinded nurse and pharmacist.

The IIH Pressure Med participants will be allocated to treatment order also by list randomisation.

8.8.1.4. Blinding

The trial will be conducted double blind. Data and laboratory analysis will be performed by blinded staff. Trial treatment and placebo will be administered, and training given by, an unblinded nurse to maintain blinding of the clinical team.

Unblinding will occur for emergency medical reasons. This will occur at the request of the co-investigators or PI. This decision will be documented in the CRF. Participants will be withdrawn from the active treatment arm if deemed necessary by the investigators. Where possible, the participant will be followed up in the trial if they are happy to do so.

8.9. Trial treatment / intervention

8.9.1. Treatment Part 1 – Exenatide

Treatment arm

Treatment arm participants will be administered Exenatide s/c. Exenatide is not licenced for the treatment of IIH, but is presently licenced for the treatment of diabetes.

Control arm

Control arm participants will receive normal saline placebo.

All Participants

All participants will receive proxymetacaine 0.5% eye drops. 1 drop to the eye to be measured for central corneal thickness, see section 8.4.

8.9.1.1. Treatment Supply and Storage

Treatment Supplies

Treatments will be supplied by the pharmacy at University Hospitals Birmingham NHS Trust in accordance with normal clinical procedure. Exenatide will be sourced from AstraZeneca UK Limited.

Packaging and Labelling

UHB Pharmacy will label and package as per UHB protocol.

Drug Storage

Drugs will be stored in pharmacy to the manufacturer's requirement until needed, they will be transferred to the CRF in ambient conditions. Storage and accountability will follow UHB protocol.

8.9.1.2. Dosing Schedule

Treatment arm

Treatment arm participants will be administered Exenatide s/c. On visit 1 they will receive a single 20mg dose whilst undergoing ICP monitoring. Subsequently they will receive 10mg BD dosing for the duration of the study.

Control arm

Control arm participants will receive normal saline placebo during the visit 1 as 1ml s/c injections. Subsequently they will receive BD dosing of normal saline placebo 0.5mls.

8.9.1.3. Drug Interaction or Contraindications

The use of medication acting through GLP-1 agonism or DPP-4 inhibition will exclude these potential participants from the trial.

Participants may not be taking acetazolamide or topiramate therapy or other drugs used to treat IIH during the trial. Potential participant will need to cease taking topiramate, acetazolamide or diuretics and undergo a wash-out period of 1 month prior to eligibility. The recent Cochrane Review[58] found no clear consensus as to the effectiveness of any drug in IIH. Patients will only be withdrawn from

medication if it is safe to do so regarding their IIH or other relevant condition. Other drugs used to treat headache (e.g. analgesia, headache prophylaxis) may be taken.

Other concomitant medications for other co-morbidities are permitted.

Pregnancy or imminently planning to conceive will necessarily exclude potential participants as Exenatide is contra-indicated. Potential participants will undergo a pregnancy test at enrolment and baseline.

8.9.1.4. Accountability Procedures

Treatment arm participants will return their used injectors which will be inspected to ascertain compliance.

8.9.1.5. Treatment Modification

In the event that the patient finds the expected side-effects problematic, the dose will be reduced for a short period at the discretion of the investigator and with the patient's agreement. This will be recorded in the CRF and medical notes.

8.9.2. Treatment Part 2 – IIH Pressure Med

Participants continuing with the IIH Pressure Med investigation will receive treatment with 5 drugs in rotation as set out in 8.2.2. The drugs will be acetazolamide, spironolactone, furosemide, amiloride and topiramate.

8.9.2.1. Treatment Supply and Storage

Treatment Supplies

Treatments will be supplied by the pharmacy at University Hospitals Birmingham NHS Trust in accordance with normal clinical procedure.

Packaging and Labelling

UHB Pharmacy will label and package as per UHB protocol.

Drug Storage

Drugs will be stored in pharmacy to the manufacturer's requirement until needed, they will be transferred to the CRF in ambient conditions. Storage and accountability will follow UHB protocol.

8.9.2.2. Dosing Schedule

Each drug will be given open label for 2 weeks; one week of titration followed by 1 week at standard treatment dose. All doses are standard clinical doses. The doses used do not require weaning at cessation. Renal function and urine HCG will be checked prior to commencing the investigation. There will be a minimum 1-week washout period between any two doses. Where a patient has a prior allergy or intolerance to a drug this will be omitted. If a titration is not tolerated patients will stop at the maximum tolerated dose.

- Acetazolamide: Patients will take 500mg BD PO immediate release for 7 days, followed by 1g BD for 7 days. The first dose will be given whilst undergoing ICP monitoring via telemeter.
- Spironolactone: Participants will take 100mg OD PO for 7 days, followed by 200mg OD for 7 days. The first dose will be given whilst undergoing ICP monitoring via telemeter.
- Amiloride: Participants will take 10mg OD PO for 14 days. The first dose will be given whilst undergoing ICP monitoring via telemeter.
- Furosemide: Patients will take 40mg OD PO for 7 days, followed by 80mg OD for 7 days. The first dose will be given whilst undergoing ICP monitoring via telemeter.
- Topiramate: Participants will take 25mg BD PO for 4 days, followed by 25mg mane/50mg nocte for 3 days followed by 50mg BD for 7 days. The first dose will be given whilst undergoing ICP monitoring via telemeter.

8.9.2.3. Drug Interaction or Contraindications

Conditions will apply as per main trial (section 7.1.3)

8.9.2.4. Accountability Procedures

Participants will return their medication supply which will be inspected to ascertain compliance.

8.9.2.5. Treatment Modification

In the event that the patient finds the expected side-effects problematic, the dose will be reduced for a short period at the discretion of the investigator and with the patient's agreement. This will be recorded in the CRF and medical notes. Where patients have an existing intolerance to a drug the

investigator will discuss that treatment round with the patient. Where previous intolerance is severe that treatment round will be omitted.

8.10. Trial procedures and assessments

8.10.1. Summary of assessments

TABLE 30 - ASSESSMENT SUMMARY

	TRIAL PERIOD											
	Enrolment	Surgery	Baseline (hours)						Trial treatment period	Week 2	Week 12	IIH Pressure Med
TIMEPOINT**	*t-1 month*		-1	0	2 5	6	11	24	*0-12 weeks (+/- 7 days)*	*(+/- 7 days)*	*(+/- 7 days)*	*Week 13+*
ENROLMENT:												
Eligibility screen	X											
Trial consent	X											
IIH PM Consent												X
Headache diary	X								X			X
INTERVENTIONS:												
ICP monitor		X										
Exenatide (treatment arm)				X				X	X	X	X	
Control normal saline				X				X	X	X	X	
Topiramate												X
Amiloride												X
Furosemide												X

Spironolactone												X
Acetazolamide												X
ASSESSMENTS:												X
ICP monitoring			X	X	X	X	X	X		X	X	X
IOP measure			X	X	X	X	X	X			X	
Headache severity			X	X	X	X	X	X		X	X	X
Weekly weight			X						X	X	X	X
Cannula			X								X	
Blood sampling			X	X	X	X	X	X			X	X
Urine HCG test	X		X									X
DEXA			X								X	
Lumbar catheter (optional)			X									
Jugular venous sample (optional and max twice)		X	X								X	
Sleep monitor							X					
OCT			X			X		X		X	X	X
Cognitive			X			X				X	X	X
HIT-6 SF-36			X								X	

8.10.2. Schedule of Assessments

8.10.2.1. Trial Part 1 - Exenatide

Enrolment visit

See 8.6.1.2 for procedure. Urine HCG test will be performed. Following screening participants will complete a headache diary for 1 month prior to surgical implantation.

Surgery visit

All participants will attend UHB for insertion of a telemetric ICP monitor under local or general anaesthesia. Anaesthetic decisions will be undertaken by the anaesthetic team in consultation with the participant. Telemetric monitor is inserted via a scalp incision and burr-hole with the catheter inserted into the brain parenchyma of the right frontal lobe. Where a participant has consented to an optional jugular venous blood sample being taken this will also be performed on the day, potentially under anaesthesia in consultation with the surgical and anaesthetic teams. Headache scores will be recorded.

Baseline visit

Participants will attend the clinical research facility at UHB, fasted, after a minimum 1-month headache diary period and surgery. Consent will be re-affirmed verbally and noted. Basic medical history, examination and clinical measurements will be recorded, urine HCG test, visual assessments (as per below section 8), questionnaires (HIT-6 and SF-36) and cognitive testing will be completed. DEXA will be completed on the day (or at the surgical visit).

Participants will go on to have a cannula placed to allow blood sampling. A minimum 1-hour telemetric baseline pressure will be recorded and baseline blood samples will be collected.

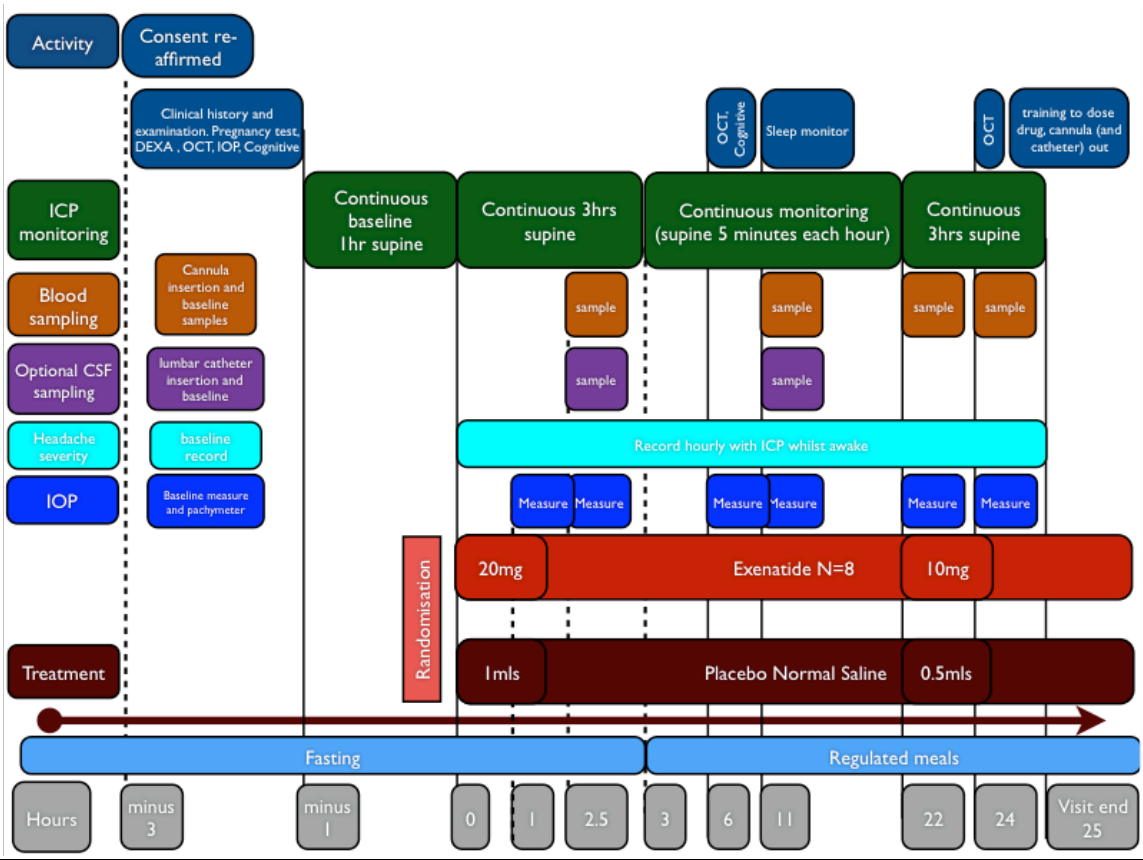
Participants will be randomised and will then be administered Exenatide or normal saline according to allocation with investigator and patient blinded. Medication will be administered by an unblinded nurse.

ICP will be recorded continuously. Recordings will be taken in a recumbent position for a minimum of 5 minutes every hour. Headache score will be recorded with each defined ICP measure.

Optional lumbar catheter will be inserted at the start of the day with sampling of CSF at baseline, 2.5 hours, 11 hours and 24 hours after drug administration. Where a participant has consented to an optional jugular venous blood sample being taken this will also be performed on the day (unless taken at the surgical visit).

OCT and cognitive testing will be repeated at 6 hours after drug administration. IOP and Central Corneal Thickness (CCT) will be recorded at baseline and IOP will be measured at 1, 2.5, 6, 11, 22 and 24hrs.

FIGURE 29 - BASELINE VISIT SCHEMA



Home ICP Monitoring

Participants will optionally be able to monitor ICP at home for periods up to a week including in an ambulatory fashion. Where this option is taken a monitoring device will be provided and utilised as per the UHB Clinical Home Monitoring Proforma. This maybe conducted prior to baseline, between visits 1 and 2 and after visit 2 as per patient preference.

Week 2

Participants will attend the clinical research facility at UHB after 2 weeks treatment (+/- 7 days). They will undergo 2.5 hours of ICP monitoring and will complete a headache severity score, OCT, blood samples and cognitive testing.

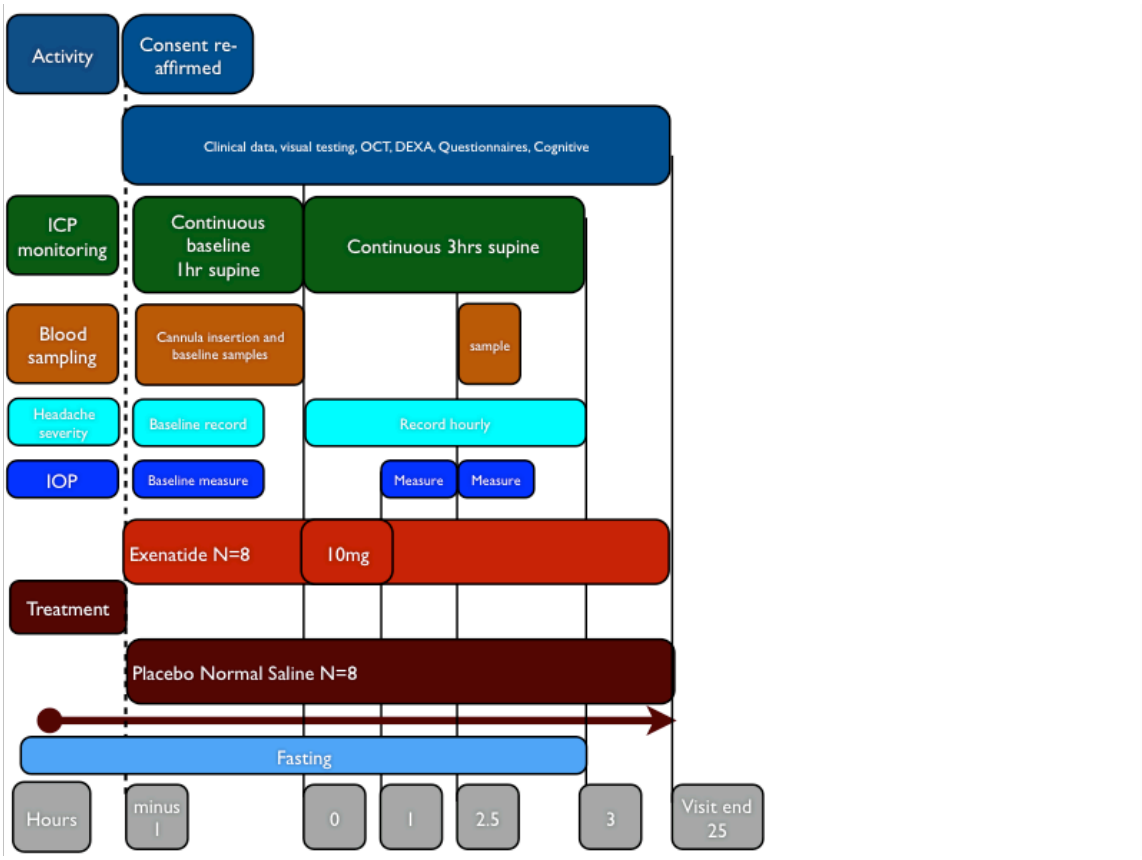
Week 8

Participants will be asked to complete a further 1 month headache diary prior to the end of the trial period.

Week 12

Participants will attend the clinical research facility at UHB after 3 months treatment (+/- 7days if required). They will undergo ICP recording and blood sampling. Visual testing as per below will be completed and repeated clinical measurements, headache scores, HIT-6 and SF-36 questionnaires will be completed, DEXA, IOP and cognitive testing. IIH symptoms will be recorded. Headache scores will be completed alongside ICP measures. Clinical data will be recorded on the Visit 2 CRF. Where a participant has consented to an optional jugular venous blood sample being taken this will also be performed on the day. IIH Pressure Med PIS (appendix C) will be offered.

FIGURE 30 - WEEK-12 VISIT SCHEMA



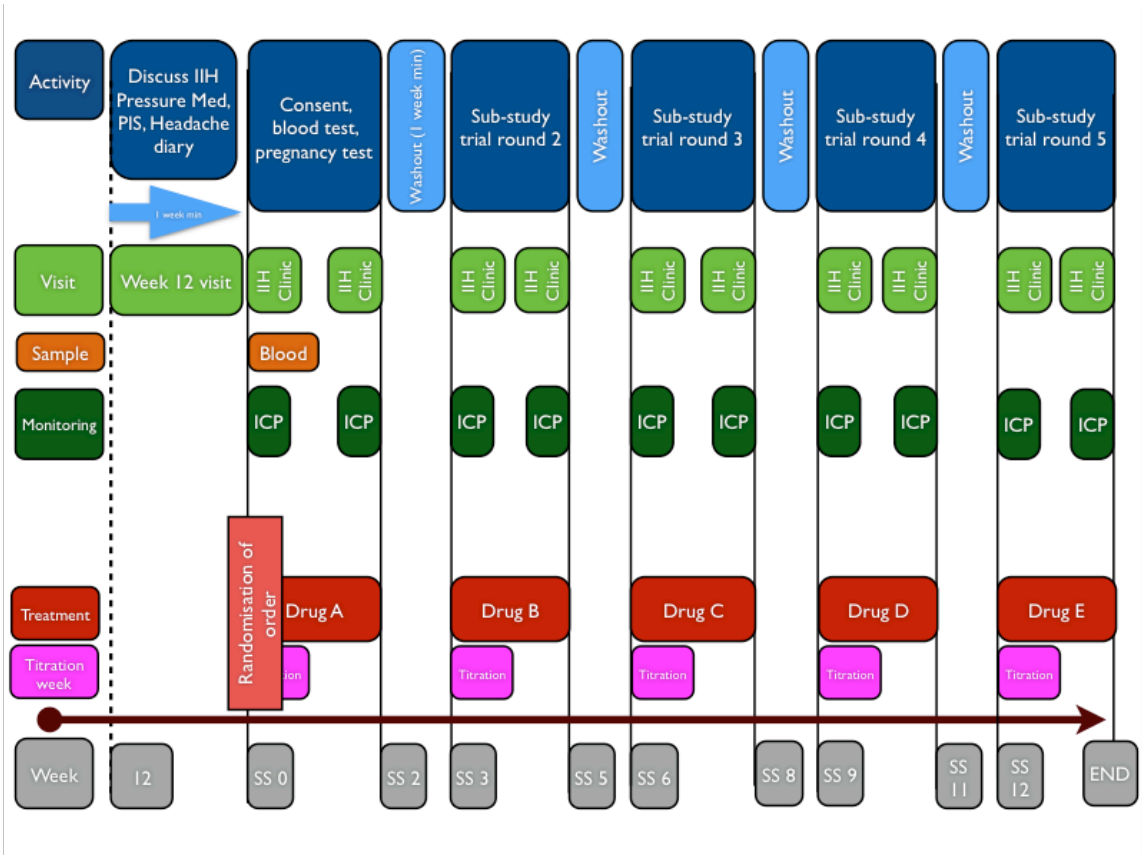
8.10.3. Trial Part 2 – IIH Pressure Med

Participants will be offered enrolment to the IIH Pressure Med investigation following the first part of the trial as set out in sections 5 and 6.2. Participants will be allocated to a treatment rota slot by randomisation (6.2). Participants will attend for visits as set out in figure 5. Participants will have renal function and repeat urine HCG checked at the start of this part of the trial and will complete a headache diary prior to each visit (appendix H).

Participants will attend the IIH clinic at UHB for short visits at the start and end of each 14-day treatment period. There will be a minimum 7-day washout period between treatment periods. They

will undergo pressure recording supine for 1.5-hours with the home pressure monitoring procedure (Utilising UHB Clinical pro forma) performed at the start and end and headache severity scores completed and cognitive testing. The trial medication will be administered at 30 minutes. IIH symptoms will be recorded. Clinical data will be recorded on the IIH Pressure Med CRF.

FIGURE 31 - IIH PRESSURE MED SCHEMA



8.11. Trial Procedures

Participants will undergo the assessments at the Wellcome Trust Clinical Research Facility (WTCRF), which lies within the hospital campus, as outlined above for the baseline visit.

- **Pregnancy Test:** A urine pregnancy test will be undertaken (HCG).

- **Clinical Data:** This visit will include recording of demographic data, and current medication (acetazolamide, topiramate, hormonal contraception, diuretics, and over the counter painkillers).

- **Clinical Measurements:** Blood pressure, heart rate, waist and hip measures and ratio, height, and weight (footwear removed) and body composition using Tanita scales.

    - Height will be measured to the nearest 0.1 cm with a rigid stadiometer
    - Body weight will be measured in light indoor clothing to the nearest 0.1 kg
    - Waist circumference will be recorded to the nearest 0.1 cm at the mid-point between the lower costal margin and the level of the anterior superior iliac crest
    - Hip circumference will be recorded to the nearest 0.1cm, from the widest point of the hips and the maximum protrusion of the gluteal muscles.
    - Brachial blood pressure will be measured as recommended by the British Hypertension Society

(http://www.bhsoc.org/how_to_measure_blood_pressure.stm) three times in the sitting position using standardised Welsh Alyn or Dinamap blood pressure monitors. The average of the second and third blood pressure readings will be recorded

- **IIH Symptoms:** The presence or absence of symptoms attributed to IIH (and not from pre-existing conditions) will be formally recorded (pulsatile tinnitus, visual loss, diplopia (excluding that occurring from a longstanding squint), visual obscurations, and headache).

- **Headache:** Participants will complete a daily headache diary in the month before visit 1 and before visit 2, which will evaluate the headache frequency, severity and frequency of analgesic days and migraine days). Headache phenotype (according to criteria from the International Headache Society) will be assessed. Headache associated disability will be evaluated using the Headache Impact Test-6 score (HIT 6)[166] and Short form 36 (RAND-36)[167] analgesic use will be recorded alongside the headache diary. Severity and frequency of headaches will be assessed. Headache scores will also be assessed during visits 1 and 2 and during the optional home ICP monitoring if applicable.

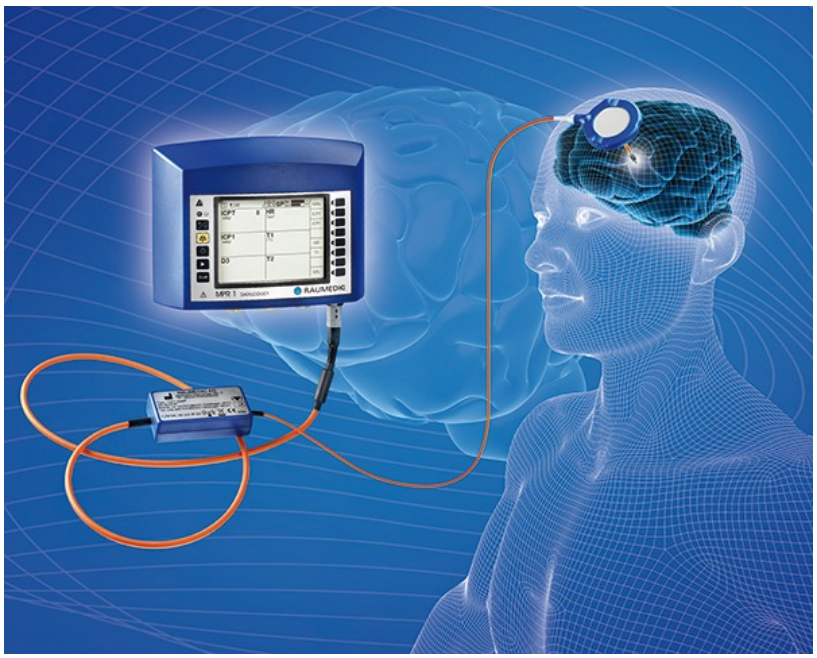
- **Blood sampling:** The participant will undergo blood sampling for analysis, at visit 1 and 2 this will be conducted via a venous catheter inserted as per normal clinical practice. Detail in Sampling Pro forma (appendix F).

- **Telemetric ICP catheter:** A Raumedic Neurovent P-tel telemetric catheter will be inserted under local or general anaesthesia as per manufacturers and normal clinical procedure. The device is inserted via a scalp incision and burr-hole with the probe tip inserted into the brain parenchyma of the right frontal lobe. The skin is closed over the monitor. Subsequent removal of the probe is also performed surgically and will be done when requested by the patient or as advised by the clinical team. In some cases the monitor may be left in after the close of the trial to facilitate clinical management as advised by the treating doctor.

FIGURE 32 - P-TEL TELEMETRIC CATHETER

- **Telemetry monitor**: Telemetric ICP recording is performed by the external placement of the telemetric coil over the monitor and held in place physically by a bandage. There is no discomfort in monitoring. The monitoring occurs via wired connection to a monitor.

FIGURE 33 - RAUMEDIC MPR-1



- **Visual Testing:**

    - LogMAR: log of the minimum angle of resolution, will be recorded using a chart to assess visual acuity.

- HVF: automated perimetry (Humphrey 24-2 central threshold) will be performed to measure the visual field mean deviation.

- OCT: Optic Coherence Tomography will be performed. Scans will include multi-colour imaging, Infra-red reflectance, macula and disc volume scans and retinal nerve fibre layer.

- IOP: Intra-ocular pressure will be measured using an iCare tonometer. This utilises a rebound measurement principle and does not require anaesthetic drops and is well tolerated.

- **Sleep Monitor**: Patients will undergo sleep monitoring overnight during visit 1 using an ApneaLink Air, non-invasive sleep monitor.

- **DEXA Scan:** A DEXA scan will be performed to accurately assess body composition. DEXA scanning involves exposure to a small quantity of radiation – equivalent to 9 hours of the daily background radiation that we are all continuously exposed to.

- **Cognitive tests**: Cognitive testing will be carried out using a battery of computer/tablet based cognitive tests. Verbal working and short-term memory and attention will be tested.

- **Meals**: patients will attend both visits fasted from midnight. To standardise subsequent intake for visit 1 standard meals will be provided with consistent ratios of constituents. The meals will be standard ready meals supplied by 'The Natural Low-Carb Store'. Meals will be provided as per figure 3. The week 12 will not require a regulated meal but food will be provided following close of the visit.

8.11.1. Sub-study Procedures

- **Intra-ocular pressure (IOP):** IOP in one eye will be measured supine utilising an iCare Pro device. This uses a probe to measure the IOP by tonometry. The procedure causes as small amount of discomfort but no analgesia is required and the procedure is repeatable over the course of the study visit. This will be measured at baseline, 1hr, 2.5hrs, 6hrs, 11hrs, 22hrs, 24hrs.

- **Central Corneal Thickness:** This is required to be measured in order to interpret the IOP readings. This is measured using a pachymeter following topical anaesthesia of the cornea as is usual clinical practice. This will be recorded at baseline.

- **Lumbar catheter** (LC)(optional): LC will be performed with the participant breathing steadily in the left lateral position; legs extended greater than 90^{o} at the hip, in accordance with normal clinical procedure. CSF discharged as part of the procedure will be collected as the baseline sample. Where patients are not undergoing sampling the catheter will be stopped off allowing mobilisation. CSF sampling will be kept to minimum volume, approximately 1ml at each sample. This volume will be replaced with Normal Saline to reduce effects of volume depletion on pressure.

- **Jugular venous blood sample (optional):** A jugular venous blood sample may be taken utilising the usual clinical technique under ultrasound guidance. This will be used to measure levels of CGRP. Up to 2 samples may be taken from a participant, one at the surgical visit (potentially during anaesthesia) or baseline and one at 12 weeks, or at other visits as per the participants request with the aim of sampling once with a severe headache (score 8-10/10 VRS) and once at another timepoint.

8.12. Adverse Event Reporting

8.12.1. Reporting Requirements

The collection and reporting of Adverse Events (AEs) will be in accordance with the Research Governance Framework for Health and Social Care and the requirements of the National Research Ethics Service (NRES). Definitions of different types of AEs are listed in the table of abbreviations and definitions. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the trial participant this should be documented in the source data with reference to the protocol.

8.12.2. Adverse Events

AEs can be encountered in participants receiving investigational products. The AEs will be recorded.

8.12.3. Serious Adverse Events

Investigators will report AEs that meet the definition of an SAE, as described in the Abbreviations and Definitions at the end of this protocol. SAEs relating to medical devices will be reported following standard requirements and procedures regarding medical devices.

8.12.4. Events that do not require reporting on a Serious Adverse Event Form

The following are regarded as expected SAEs for the purpose of trial and should not be reported on an SAE form. These events should be reported on the adverse event form instead.

- Exacerbations of the patients IIH symptoms unless significant and sustained for 2 weeks.

- Elective and planned admissions unrelated to the trial.

8.12.5. Monitoring pregnancies for potential Serious Adverse Events

There is a possible risk of congenital anomalies or birth defects in the offspring of participants as a result of their participation in the trial. The outcome of pregnancies of participants will therefore be monitored in order to provide SAE data on congenital anomalies or birth defects. As previously stated, pregnancy is an exclusion criterion and pregnant participants will be withdrawn from the trial.

In the event that a participant becomes pregnant during the SAE reporting period a pregnancy notification form will be completed and returned to the Trials Office. Details of the outcome of the pregnancy will be provided on a follow-up pregnancy notification form and an SAE Form will be completed.

8.12.6. Reporting period

Details of all AEs (except those listed above) will be documented from the date of commencement of protocol defined treatment until 7 days after the administration of the last treatment for the main trial.

SAEs that are judged to be at least possibly related to the medication must still be reported in an expedited manner irrespective of how long after investigational product administration the reaction occurred.

8.12.7. Reporting Procedure

8.12.7.1. Adverse Events

AEs are commonly encountered in participants receiving Exenatide. As the safety profiles of the medications used in this trial are well characterised, only Adverse Reactions (ARs) experienced during treatment will be reported. Surgical adverse events will also be reported.

8.12.7.2. Serious Adverse Events

AEs defined as serious, and which require reporting as an SAE should be reported on an SAE Form. When completing the form, the Principal Investigator will be asked to define the causality and the severity of the AE.

On becoming aware that a participant has experienced an SAE, the Principal Investigator (or delegate) must complete, date and sign an SAE Form. SAEs not judged Unexpected and Related will be collated and reported on via the Annual Progress Report sent to the REC.

8.12.7.3. Provision of follow-up information

Participants should be followed up until resolution or stabilisation of the event. Follow-up information should ideally be provided on a new SAE Form.

8.13. Reporting to the Research Ethics Committee

8.13.1. Unexpected and Related Serious Adverse Events

The PI will report all events categorised as Unexpected and Related SAEs to the Research Ethics Committee (REC) within 15 days.

A copy is also sent to the University of Birmingham Research Governance Team at the time of sending out the Unexpected and Related Serious Adverse Event.

8.13.2. Other safety issues identified during the course of the trial

The REC will be notified immediately if a significant safety issue is identified during the course of the trial. The University of Birmingham Research Governance Team will also be informed at the time that the REC is informed.

8.14. Data Handling and Record Keeping

8.14.1. Source Data

In order to allow for the accurate reconstruction of the trial and clinical management of the subject, source data will be accessible and maintained.

8.14.2. CRF Completion

Data reported on each Case Report Form will be consistent with the source data and any discrepancies will be explained. Staff delegated to complete CRFs will be trained to adhere to standard operating procedure.

In all cases it remains the responsibility of the PI to ensure that the CRF has been completed correctly and that the data are accurate. The completed copies will be filed in the Site File.

8.14.3. Data Management

This trial will collect personal data about participants. Participants will be asked to consent to this. The data will be entered onto a secure computer database according to University security and quality policies and procedures.

Any relevant data to be processed will be anonymised as per UHB policy. All personal information obtained for the trial will be handled and stored in accordance with the Data Protection Act 1998, held securely and treated as strictly confidential.

Participants will be identified using only their unique study number and date of birth in mmm/yyyy format on CRFs and correspondence.

Samples will be stored as described above. They will be identified by participant study number and a code describing the sample. This will be recorded on a Sample Log at the visit.

The Principal Investigator will keep their own trial file log which link participants with anonymised CRFs. The Investigator must maintain documents in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

All staff involved in the IIH:Pressure trial (clinical, academic) share the same duty of care to prevent unauthorised disclosure of personal information. No data that could be used to identify an individual will be published.

8.14.4. Archiving

In line with MRC guidelines and UoB Code of Practice for Research, once data collection is complete on all participants, all data will be stored for at least 10 years (but ideally not less than 20 years). Any queries or concerns about the data, conduct or conclusions of the trial can also be resolved in this time. Limited data on the participants and records of any adverse events may be kept for longer if recommended by an independent advisory board.

Trial data will be stored within the UoB under controlled conditions for at least 3 years after closure. Long-term offsite data archiving facilities will be considered for storage after this time and have been costed into the grant.

The Principal Investigator is responsible for the secure archiving of essential trial documents as per their NHS Trust policy. All essential documents will be archived for a minimum of 5 years after completion of trial.

8.15. Quality control and quality assurance

8.15.1. Site Set-up and Initiation

All participating Investigators will be asked to sign the necessary agreements and supply a current Curriculum Vitae (CV) to the Trials Office. All members of the research team will also be required to sign a site signature and delegation log. Prior to commencing recruitment, the site will undergo a process of initiation and will have completed Good Clinical Practice (GCP) training. Key members of the site research team will be required to attend a meeting covering aspects of the trial design, protocol procedures, Adverse Event reporting, collection and reporting of data and record keeping. An Investigator Site File containing essential documentation, instructions, and other documentation required for the conduct of the trial will be provided.

8.15.2. Monitoring

Monitoring will be carried out as required.

8.15.3. Audit and Inspection

The Principal Investigator will permit trial-related monitoring, quality checks, audits, ethical reviews, and regulatory inspection(s) at their site, providing direct access to source data/documents. The Principal Investigator will comply with these visits and any required follow up.

8.15.4. Notification of Serious Breaches

The sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial as per UoB standard practice.

8.15.5. End of Trial Definition

The end of trial will be 30 days after last data capture. The last data capture will be the final visit of the final participant. The PI will notify the REC the trial has ended and a summary of the clinical trial report will be provided within 12 months of the end of trial.

A copy of the end of trial notification as well as the summary report is also sent to the University of Birmingham Research Governance Team at the time of sending these are sent to the REC.

8.16. Statistical Considerations

8.16.1. Definition of Outcome Measures

8.16.1.1. Primary endpoints

See section 2.3.

8.16.1.2. Secondary outcome measures/exploratory endpoints

See section 2.3.

8.16.2. Analysis of Outcome Measures

8.16.2.1. Planned Randomisation Methodology

Participants will be randomized by a paper randomization system administered by the Clinical Trials Unit. Allocation will be 1:1

8.16.2.2. Planned Interim Analysis

Interim analysis may be performed after the first 6-10 patients. The Investigators will not partake in this analysis to maintain allocation concealment.

8.16.2.3. Planned Final Analyses

The main trial analysis will be conducted after the final visit of the final patient of the main trial. The IIH Pressure Med sub-study analysis will be conducted after the final visit of the final patient within the IIH Pressure Med sub-study.

8.16.3. Power Calculations

The study proposes to investigate the effect of GLP-1R agonist on the continuous variable, intracranial pressure (ICP) via a two-arm, randomised, study. The primary outcome will be change in ICP.

In a study of 25 patients, Sinclair et al[56] showed that the cross-sectional sample standard deviation of ICP is 4.9 – 5.1 cm H_2O, measured at baseline and immediately before and after a longitudinal intervention (low energy diet). It is felt that a reduction in ICP of 5 cm H_2O would be clinically meaningful.

Seeking significance at least 5% and power at least 90% using equal group sizes, a total sample size of 14 patients are required, i.e. 7 patients will be randomised to receive active treatment and a further 7 to receive control. This calculation assumes that the standard deviation of ICP is 5.1, the upper end of the range observed previously. [Allowing for 10% drop-put, the proposed recruitment is 8 patients per arm, and 16 patients in total]

8.17. Trial Organisational Structure

8.17.1. Sponsor

University of Birmingham is the sponsor of this trial.

8.17.2. Trial management group

The trial management group will be set-up and meet on a regular basis.

8.17.3. Finance

This is an investigator-initiated and investigator-led trial funded by the Ministry of Defence via the Surgeons General's Research Steering Group award to JLM. NIHR CRN Portfolio adoption will be applied for.

8.18. Ethical Considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care, the Data Protection Act 1998, Human Tissue Act 2008 and Guidelines for Good Clinical Practice (GCP). The protocol will be submitted to and approved by the REC prior to circulation.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

8.19. Confidentiality and Data Protection

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 1998.

Participants will always be identified using only their unique trial identification number, on the Case Report Form and correspondence between the Trials Office and the participating site.

The Investigator must maintain documents (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

Confidentiality of all participant's data will be maintained, and information will not be disclosed by which participants may be identified to any third party other than those directly involved in the treatment of the participant and organisations for which the participant has given explicit consent for data transfer. Representatives of the sponsor may be required to have access to participant's notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times.

8.20. Insurance and Indemnity

The UoB has in place Clinical Trials indemnity coverage for this trial which provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at the University's discretion provide cover for non-negligent harm to participants.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

8.21. Publication Policy

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the Investigators and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the principal investigator. Manuscripts must be submitted to the PI in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of University of Birmingham and MoD. All publications will undergo final military review by the Medical Director SG JMC in accordance with the funding terms.

9. Appendices

A Patient information sheet (PIS)

B Informed Consent Form (ICF)

C IIH Pressure Med PIS (PMPIS)

D IIH Pressure Med consent form (PMCF)

E Advert

F Sampling Pro forma

G Headache Diary

H Headache diary IIH Pressure Med

I GP/Consultant Letter

J IIH Pressure Questionnaires

K UHB ICP Proforma

IIH Pressure

The acute and chronic effects of gut neuropeptides on intracranial pressure regulation

Participant Invitation and information sheet

Invitation to take part in a clinical trial to improve the way Idiopathic Intracranial Hypertension (IIH) is treated.

You are being invited to take part in a clinical trial. Whether you take part is **voluntary**, and before you decide it is important for you to understand why the research is being done and what it will involve. Please consider the following information carefully and discuss it with others and your doctor if you wish. Do feel free to ask if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

Part 1 tells you why we are doing this trial and what will happen if you take part.

Part 2 gives you more detailed information about the conduct of the trial.

Principal Investigator: Dr Alexandra Sinclair, Secretary [redacted]
IIH Research Nurse mobile [redacted]
UHB PALS (Patient Advice and Liaison Service) Tel [redacted]

IIH: Pressure Trial No.:

☐☐☐☐

University Hospital Birmingham
NHS Foundation Trust

CONSENT FORM – Full trial consent.

Please initial box to confirm consent

The IIH Pressure Trial

1. I have read and understood the information sheet for the IIH Pressure trial (version 1.2 dated 18th July 2017). I have had the opportunity to consider the information, ask questions and these have been answered satisfactorily. ☐
2. I understand that my participation in this trial is voluntary and if I take part I am free to withdraw at any time without giving a reason, and without my medical care or legal rights being affected. ☐
3. I understand that personal information (partial date of birth (mm/yyyy)) and information about my progress will be supplied in confidence to the trial team outside of this NHS trust at the University of Birmingham (UoB) by my own doctors for use in the IIH Pressure trial. ☐
4. I understand that relevant sections of any of my medical notes may be looked at in confidence by responsible individuals from UoB, regulatory authorities or the NHS Trust, where it is relevant to my taking part in this research and to check that the trial is being carried out correctly. I give permission for these individuals to have access to my records. ☐
5. I agree to take part in the IIH Pressure trial. ☐
6. I agree to my samples and tissues, along with associated clinical data, being taken, stored and used for analysis of biomarkers to look for potential risk factors for Idiopathic Intracranial Hypertension both as part of this trial and in future related studies. Future studies on these samples outside of this trial would require Research Ethics Committee approval. I agree to these samples being moved outside of this NHS trust and stored at the University of Birmingham. ☐

Additional consent:

7. I agree to my GP being informed of my participation in the IIH Pressure trial. ☐
8. I agree that any unused samples and tissues obtained from this trial can be donated to an Idiopathic Intracranial Hypertension Biobank for future research. ☐

Optional sub-study consent:

9. I agree to participate in the headache (jugular venous blood) sub-study ☐
10. I agree to participate in the home ICP monitoring sub-study ☐
11. I agree to participate in the lumbar (LP) catheter sub-study ☐

Name of Participant	Date (dd/mmm/yyyy)	Signature
Name of Researcher	Date (dd/mmm/yyyy)	Signature

One copy to be kept in the IIH:Pressure trial site file, one for the patient, one kept with patient's notes.

IIH Pressure

IIH Pressure Med

The acute and chronic effects of gut neuropeptides on intracranial pressure regulation

IIH Pressure Part 2 IIH Pressure Med Invest gat on

Invitation to take part in a clinical trial to improve the way Idiopathic Intracranial Hypertension (IIH) is treated.

You are be ng nv ted to take part n part 2 of the IIH Pressure C n ca Tr a . Whether you take part s **voluntary**, and before you dec de t s mportant for you to understand why the research s be ng done and what t w nvo ve. P ease cons der the fo ow ng nformat on carefu y and d scuss t w th others and your doctor f you w sh. Do fee free to ask f there s anyth ng that s not c ear or f you wou d ke more nformat on. Take t me to dec de whether or not you w sh to take part.

Thank you for read ng th s.

This document te s you why we are do ng th s nvest gat on and what w happen f you take part.

To be read n conjunct on w th the IIH Pressure Part c pant Informat on Sheet.

Pr nc pa Invest gator, Dr A exandra S nc a r Secretary [redacted]
IIH Research Nurse Mob e: [redacted]
UHB Pat ent Adv ce and L a son Serv ce (PALS) Te ephone: [redacted]

Confidential once completed

IIH: Pressure Trial No.:

☐☐☐☐☐

University Hospital Birmingham
NHS Foundation Trust

CONSENT FORM

Please initial box to confirm consent

The IIH Pressure Trial – IIH Pressure Med

1. I have read and understood the information sheet for IIH Pressure Med (version 1.2 dated 18th July 2017). I have had the opportunity to consider the information, ask questions and these have been answered satisfactorily. ☐
2. I understand that my participation in this trial is voluntary and if I take part I am free to withdraw at any time without giving a reason, and without my medical care or legal rights being affected. ☐
3. I understand that personal information (partial date of birth (mm/yyyy)) and information about my progress will be supplied in confidence to the trial team outside of this NHS trust at the University of Birmingham (UoB) by my own doctors for use in the IIH Pressure trial. ☐
4. I understand that relevant sections of any of my medical notes may be looked at in confidence by responsible individuals from UoB, regulatory authorities or the NHS Trust, where it is relevant to my taking part in this research and to check that the trial is being carried out correctly. I give permission for these individuals to have access to my records. ☐
5. I agree to take part in the IIH Pressure Med part of the trial. ☐
6. I agree to my samples and tissues, along with associated clinical data, being taken, stored and used for analysis of biomarkers to look for potential risk factors for Idiopathic Intracranial Hypertension both as part of this trial and in future related studies. Future studies on these samples outside of this trial would require Research Ethics Committee approval. I agree to these samples being moved outside of this NHS trust and stored at the University of Birmingham. ☐

Additional consent:

7. I agree to my GP being informed of my participation in the IIH Pressure Med part of the trial. ☐
8. I agree that any unused samples and tissues obtained from this trial can be donated to an Idiopathic Intracranial Hypertension Biobank for future research. ☐

Name of Participant	Date (dd/mmm/yyyy)	Signature
Name of Researcher	Date (dd/mmm/yyyy)	Signature

One copy to be kept in the IIH:Pressure trial site file, one for the patient, one kept with patient's notes.


IIH
PRESSURE
IIH RESEARCH NEEDS YOU!
Do you live in or around the midlands and have Idiopathic Intracranial Hypertension (IIH) and ongoing papilloedema?
The IIH Pressure trial is investigating a new drug treatment to reduce brain pressure in IIH, which is currently used for weight loss.
We are using a new pressure monitoring device which can avoid the need for lumbar puncture and can read pressure continuously and at home.
You may be eligible for the IIH Pressure trial if you are: Female, 18-60, with IIH and have papilloedema.
Visit www.birmingham.ac.uk/iihpressure for further details on taking part.
Please note: You will be considered against the eligibility
UNIVERSITY OF BIRMINGHAM
University Hospitals Birmingham NHS
NHS Foundation Trust
CSF DISORDERS BIRMINGHAM
IIH: Pressure Advertising Poster Version 1.1 26th May 2017
This trial has been reviewed West Midlands Solihull Research Ethics Committee Ref:17/WM/0179
ISRCTN:

IIH Pressure

Sampling Proforma

The acute and chronic effects of gut neuropeptides on intracranial pressure regulation

Samp ng Proforma

IIH Pressure

Headache Diary

The acute and chronic effects of gut neuropeptides on intracranial pressure regulation

Headache d ary for comp et on by part c pant

Thank you for comp et ng th s d ary as d scussed w th the tr a team; nstruct ons enc osed.

IIH Pressure

IIH Pressure Med Headache Diary

The acute and chronic effects of gut neuropeptides on intracranial pressure regulation

Headache d ary for comp et on by part c pant

Thank you for comp et ng th s d ary as d scussed w th the tr a team; nstruct ons enc osed.

University Hospital Birmingham NHS Foundation Trust

<Doctor>
<Pract ce>
<Street>
<C ty>
<Postcode>

<Date>

Dear Dr <GP/Consu tant name>,

Re: **Name:** .

DoB: **Hospital No:** ..

Trial number: **Date Randomised:** ..

Opening Pressure:…… **Humphrey Visual Field:……**

The acute and chronic effects of gut neuropeptides on intracranial pressure regulation, the IIH:Pressure Trial

Your pat ent, named above, has agreed to take part n the IIH:Pressure tr a . Th s s a random sed, contro ed, doub e b nd tr a nvest gat ng the effect of the GLP 1 agon st drug, Exenat de, to p acebo, on ntracran a pressure.

Th s tr a w recru t 16 women w th act ve, IIH from the UK. They w be random sed and 8 part c pants w be a ocated to the Exenat de arm and 8 to the p acebo arm dur ng a base ne tr a v s t.

Part c pants w then take the a ocated treatment for 3 months and be fo owed up at another v s t. The pr mary outcome s the r ntracran a pressure after treatment.

Part c pants enro ed nto the tr a w be f tted (day case surgery) w th a Te emetr c Intracran a Pressure mon tor (Raumed c neurovent p Te), a ow ng cont nuous non nvas ve

IIH Pressure Questionnaires
SF-36 and HIT-6

The acute and chronic effects of gut neuropeptides on intracranial pressure regulation

Questionnaires for completion by participant

Thank you for completing these questionnaires as discussed with the trial team.

University Hospitals Birmingham NHS
NHS Foundation Trust

UHB Telemetric Intracranial Pressure Monitoring pro forma

This pro forma should be followed as directed by your Doctor/Nurse.

The monitoring pro forma is designed to be used in conjunction with telemetric ICP monitoring with the Raumedic p-Tel catheter and MPR1 Datalogger. You will be given instruction in setting up the device separately.

Please complete the following positions in order, please use the mark button as directed and hold each position for the time indicated. Please complete this pro forma on a daily basis whilst undertaking home monitoring unless otherwise directed. Please record date and time of sessions on the following table.

Session	Date	Time	Notes
Session 1			
Session 2			
Session 3			
Session 4			
Session 5			
Session 6			
Session 7			

Version 1.0 04/12/2017

Dr A.J.Sinclair, Dr J.L.Mitchell