IIH Pressure: a randomised, controlled, double blind physiology study of the effect of Exenatide on intra-cranial pressure

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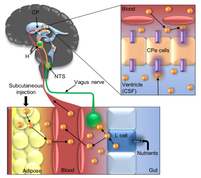
INTRODUCTION

Idiopathic intracranial hypertension (IIH) mainly affects obese women of childbearing age and is characterised by raised intracranial pressure (ICP) which causes chronic headaches and visual loss. The pathogenesis of IIH is unknown.

Exenatide is a GLP-1 agonist, current clinical use in diabetes and anti-obesity effect. We have shown Exenatide reduces ICP in an animal model. Th mechanism of action is reduction of cerebrospinal fluid secretion at the choroid plexus.[1]



AIMS

- Primary
  - To assess the biological action of a single administration of Exenatide on ICP.
  - To assess the biological action of repeated administration of Exenatide on ICP.
- Secondary Aims -to evaluate the clinical impact of lowering ICP by repeated dosing of exenatide on headache severity and frequency, and quality of life in people with active IIH.

METHOD

Randomised, placebo controlled, double-blind trial of Exenatide in women with active IIH. Participants were randomised 1:1 to Exenatide (10mcg twice daily sub-cutaneous) or placebo for 12 weeks. Telemetric, intraparenchymal ICP monitors (Raumedic)(Fig. A) recorded ICP over 12 weeks. Analysis was by hierarchical regression, significance level set at p <0.1

Prospective, randomised, placebo controlled, double blind, parallel group, explorative trial.

12 weeks

1:1

Placebo
2* daily S.C.

Exenatide
10mcg BD S.C.

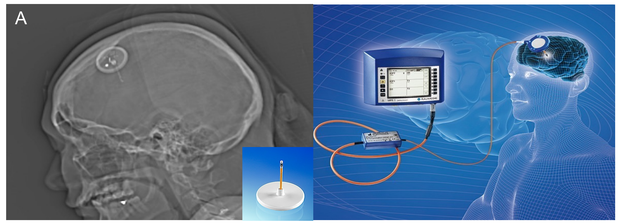
- N=16
- Telemetric ICP

Primary endpoints
Change in intracranial pressure at 2.5hrs, 24hrs and 12 weeks

Exploratory endpoints
Headache: monthly headache days, monthly analgesic days, severity, duration
Vision: visual acuity, visual field assessment, ocular coherence tomography

Inclusion
- Female 18-60
- Active IIH

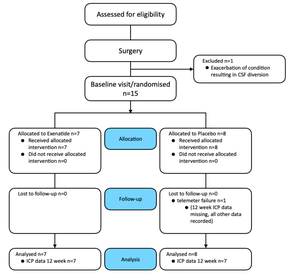
Exclusion
- Pregnant
- Significant co-morbidity
- CSF diversion procedure
- Therapy with intracranial pressure lowering drugs within 1 month
- GLP-1 or DPP-4 inhibitor



RESULTS

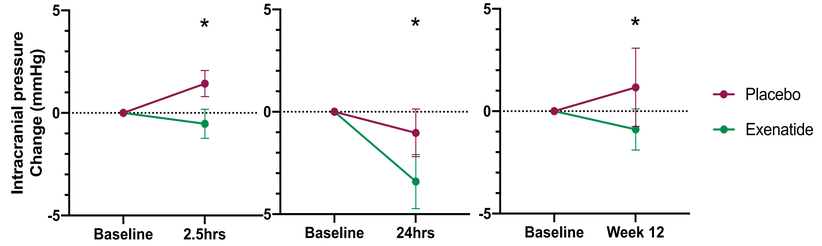
1 – Baseline data

	All	Exenatide	Placebo
Number	15	7	8
Age	28 (9)	28 (13)	28 (6)
BMI (kg/m2)	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 (papilloedema) (worst eye) *	2 (2-3)	2 (2-2)	2.5 (2-3)



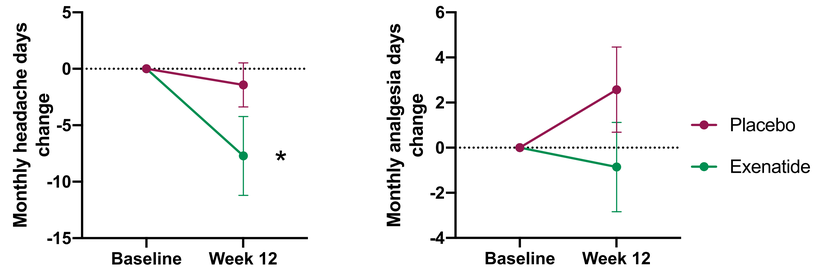
16 female patients were recruited to the IIH Pressure study, (consort). One participant was withdrawn before randomisation, due to exacerbation of their condition necessitating escalation of their management. In one participant the telemeter failed at the 12-week visit and hence ICP data is missing at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

2 - Primary Outcomes – Intracranial pressure



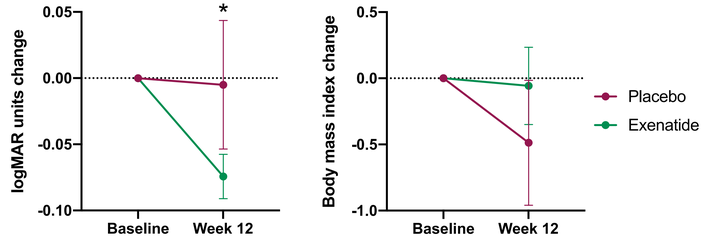
Following drug administration there was an acute and significant fall in ICP. At 2.5 hours ICP fell by 4.2 (1.9) (mean (SD) mmHg), p=0.031, and at 24 hours by 4.7 (2.1), p=0.030. The effect was sustained at 12 weeks with an ICP reduction of 4.6 (2.5), p=0.058.

3 - Headache outcomes



After 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 monthly analgesia days, Exenatide -0.9 (5.2) days, p=0.680, placebo 2.4 (5.1) days, p=0.254.

4 – Visual acuity BMI



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 BMI in either Exenatide or placebo arm over the course of the trial, p=0.859.

CONCLUSIONS

- Exenatide significantly reduces intracranial pressure, acute and longstanding efficacy
- Monthly headache days and visual acuity improved in exenatide group
- Intracranial pressure effect is not mediated by weight loss

This is this first trial of a new drug treatment for raised intra-cranial pressure that significantly reduces ICP

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REFERENCES

1. Botfield HF, Uldall MS, Westgate CSJ, Mitchell JL, Hagen SM, Gonzalez AM, Hodson DJ, Jensen RH, Sinclair AJ. A glucagon-like peptide-1 receptor agonist reduces intracranial pressure in a rat model of hydrocephalus. Sci Transl Med. 2017 Aug 23;9(404):eaan0972. doi: 10.1126/scitranslmed.aan0972.