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Shunting for idiopathic normal pressure hydrocephalus (Protocol)

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TABLE OF CONTENTS

[Intervention Protocol]

Shunting for idiopathic normal pressure hydrocephalus

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To determine the effect of cerebrospinal fluid (CSF) shunting versus no CSF shunting in people with idiopathic normal pressure hydrocephalus (iNPH).

To determine the frequency of adverse effects of CSF shunting in iNPH

BACKGROUND

Description of the condition

Normal pressure hydrocephalus (NPH) is a clinical syndrome of gait apraxia, cognitive impairment, and urinary incontinence (Adams-Hakim triad) due to communicating hydrocephalus with normal cerebrospinal fluid (CSF) pressure (Hakim 1965a). Before Hakim and Adams' original description in 1965, hydrocephalus was only recognised to occur due to acute intracranial illness, such as an expanding tumour or bleeding, where people presented acutely, with signs and symptoms of raised CSF pressure, such as headache and visual loss.

In NPH, it is thought that an initial increase in intracranial pressure causes the intracerebral ventricles to expand and change shape, until a new compensated state occurs, where the CSF pressure is relatively normalised (Adams 1965a; Hakim 1965a). When intracranial pressure rises further, this equilibrium decompensates and leads to a subacute presentation of the NPH clinical syndrome (Hakim 1965a).

NPH can occur when there is a clear cause for the initial rise in intracranial pressure, such as after brain trauma or CNS inflammation (Hakim 1965a). It can also occur in the elderly population (> 60 years) without a clear cause, where it is known as idiopathic NPH (iNPH (Adams 1965a)). Even in iNPH, reducing the intraventricular pressure by permanent CSF diversion (shunting) has been reported to improve symptoms (Adams 1965a; Kazui 2015a; Tisell 2011a).

However, there are no known pathognomonic histological features to characterise the disease (Espay 2017a). Problematically, the current diagnostic gold standard is a (variably defined) positive response to definitive CSF shunting, which is also the proposed treatment (Espay 2017a). Controversy regarding iNPH as a clinical entity remains, as not everyone with iNPH responds to CSF shunting (Malm 2006a).

Enlargement of the cerebral ventricles (ventriculomegaly) was historically the sole radiological indicator of NPH (Kitagaki 1998a), but this is now understood to be common in normal ageing individuals; more than 20% of those over 70 years fulfil the criteria for ventriculomegaly (Jaraj 2017). Several groups noticed specific morphological changes in those with shunt-responsive iNPH, such as disproportional enlargement of the Sylvian fissures (Hashimoto 2010; Kitagaki 1998a; Kockum 2018). These iNPH-specific magnetic resonance imaging (MRI) features have been further developed, and have been incorporated into recent diagnostic criteria for iNPH (Nakajima 2021). iNPH radiological grading scales are used to identify those who definitely do not have shunt-responsive iNPH (Kockum 2020a).

Potential disease mechanisms in iNPH are poorly understood, but reduced CSF conductance, reduced pulse pressure across the cerebral aqueduct, reduced CSF production and turn-over, impaired regional cerebral perfusion, impaired glymphatic drainage, and build-up of toxic metabolites have all been reported in iNPH (Bradley 2015a; Momjian 2004a; Ringstad 2017a; Silverberg 2003a).

Cilia are present in the CNS, and have an active role in the development of choroid and ventricular function (Banizs 2005). It is well understood that dysfunction of CNS cilia is associated with hydrocephalus (Banizs 2005; Louvi 2011). Autosomal dominant mutations in the CFAP43 gene, which encodes a cilial protein, are usually seen in primary cilial dyskinesia, but have recently been found in a Japanese person with familial NPH (Morimoto 2019a). The further discovery that CWH43 mutations can induce hydrocephalus in mice, which have reduced ventricular cilial density, and that these mutations are over-represented in people with purported idiopathic NPH, suggest that CNS cilial function is important in the development of iNPH (Yang 2021).

Diabetes mellitus, obstructive sleep apnoea, and schizophrenia are all more common in people with iNPH than their age-matched controls, but the nature of these relationships is not known (Hudson 2019; Román 2018; Vanhala 2019).

Co-morbid neurodegenerative disease is also common in people with iNPH; there will usually be evidence of neurodegenerative disease at post-mortem (Cabral 2011). However people with possible iNPH who have CSF or neuropathological findings consistent with Alzheimer's disease, do not respond differently to CSF removal or shunting (Müller-Schmitz 2020; Yasar 2017). As the radiological features specific to iNPH are thought to develop over time in ageing individuals, from an asymptomatic to symptomatic stage (Kimihira 2020a), it is not surprising that they are also seen in the elderly population who present with symptoms of neurodegenerative disease (Ohara 2020). The relationship between NPH, ageing, and neurodegenerative disease is likely to be complex.

Description of the intervention

CSF shunting is the process during which the CSF pressure is reduced by surgically inserting a catheter to divert CSF to an area of lower pressure. Initial studies in NPH used ventriculoatrial (VA) shunts, which relocated CSF to the right atrium of the heart (Hakim 1965a). Due to potentially serious cardiac complications of VA shunting (Lam 1997), lumboperitoneal (LP) or ventriculoperitoneal (VP) shunts are now used routinely, diverting CSF to the peritoneum (Kazui 2015a; Tisell 2011a). Ventriculopleural (VPl) shunts may be considered when VP or LP shunts are contraindicated (Craven 2016). Third ventriculostomy is another shunting procedure, during which a hole is created to divert CSF from the third ventricle of the brain to an extra-parenchymal CSF space.

How the intervention might work

In NPH, cerebral ventricles change shape to accommodate for a rise in pressure and frontal lobes become compressed causing a classical appearance with a tight, high convex, and a reduced callosal angle, with widening of the sylvian fissures (Kitagaki 1998a). Pathology in the frontal cortical and subcortical regions is known to cause cognitive decline, gait apraxia, and urinary symptoms, which are seen in iNPH (Hakim 1976; Ogino 2006; Sakakibara 2008). The amount of mass effect (or change in shape due to pressure effects) seen in the superior cortical structures appears to correlate with the effect of CSF shunting (Narita 2016a). In people with NPH, a reduction of CSF conductance and periventricular cerebral perfusion are also seen with lumbar infusion testing (Børgesen 1982; Momjian 2004a); the former has an inverse relationship to the effect of CSF shunting (Børgesen 1982). Therefore, there are plausible mechanisms to explain how decompensation of an NPH state can cause Hakim's triad of

symptoms, and how permanent CSF diversion can help normalise the effects of pressure, and improve symptoms of people with iNPH.

Why it is important to do this review

Because of the evolution of clinical and radiological definitions of iNPH over time, there is a lack of high-quality, standardised epidemiological data (Zaccaria 2020). Prevalence has been estimated as 29/100,000, with an incidence of 7.3/100,000/year, rising to 1.2/1000 in those over 70 years of age (Zaccaria 2020). However, cardinal symptoms of iNPH are both non-specific and common (Macki 2020a). High quality, community-based, prospective studies show that up to 3.7% of those over 65 years of age fulfil the clinical criteria for iNPH, and on cranial imaging, show radiological features specific to iNPH (Andersson 2019a). In the UK and Ireland, between 2004 and 2013, 14% of CSF shunts (2173) were inserted for iNPH, and the number seems to be rising (Fernández-Méndez 2019). Therefore, people commonly present to clinicians with possible iNPH, and many have surgery. There is a need for clear evidence about the role of CSF shunting.

Several reviews have concluded that there is a role for CSF shunting in iNPH (Giordan 2018a; Halperin 2015; Hebb 2001a; Toma 2013a). However, there are little meta-analytic data regarding the effect size, and systematic reviews restricted to randomised controlled trials have not reached similar conclusions (Esmonde 2002a). As such, there remains uncertainty regarding iNPH management in the neurological community.

Since the last Cochrane Review of shunting in NPH (Esmonde 2002a), there have been advances in understanding specific radiological features of iNPH (Kockum 2020a; Narita 2016a), and an evolution of clinical criteria for iNPH (Nakajima 2021; Relkin 2005a). There have also been new randomised controlled trials that assess the effect of CSF shunting in iNPH, which have taken these updated criteria and imaging features into account. Thus, we consider it timely to conduct a systematic review on the effects of CSF shunting in people with iNPH, in order to help guide management decisions.

OBJECTIVES

To determine the effect of cerebrospinal fluid (CSF) shunting versus no CSF shunting in people with idiopathic normal pressure hydrocephalus (iNPH).

To determine the frequency of adverse effects of CSF shunting in iNPH

METHODS

Criteria for considering studies for this review

Types of studies

We will include only randomised controlled trials (RCTs) of the effect of shunting in idiopathic normal pressure hydrocephalus (iNPH).

People may be reluctant to participate in clinical trials in which they are at risk of not being shunted. Therefore, we anticipate that we will encounter trials with a one-arm, cross-over design, in which half of the cases will have the intervention initially, and the other half will have the intervention at a later time; such studies may be blinded or unblinded (Saper 2017). In trials of this design, there is an early post-randomisation time period when there are parallel intervention and control groups, which may be used to investigate the effect of the intervention.

Types of participants

To be eligible for this study, participants must have at least one symptom of the Adams–Hakim triad: gait apraxia, dementia, or urinary incontinence, and an Evan's index of > 0.3 on cranial imaging. Participants must be at least 60 years of age, and have a normal cerebrospinal fluid (CSF) opening pressure.

We will exclude participants with potential secondary causes of normal pressure hydrocephalus (NPH), such as previous head trauma, meningitis, or subarachnoid haemorrhage.

These criteria are consistent with the Japanese Society of Normal Pressure Hydrocephalus Guidelines (Nakajima 2021), except that we will define elevated opening pressure as > 24.5 cm of water, which is consistent with international diagnostic guidelines in idiopathic normal pressure hydrocephalus (iNPH), and normal CSF reference ranges used in other neurological fields (Mollan 2018; Relkin 2005a). We will include studies in which participants may have had only one of Hakim's triad of symptoms, to ensure we do not exclude studies conducted before current diagnostic guidelines became available, but we will use sensitivity analysis to determine the effect of including these studies (Ishikawa 2004; Relkin 2005a). Similarly, we will not restrict participants to those who have a tight, high convexity and enlarged sylvian fissures on cranial imaging, to ensure we include any RCTs conducted before these iNPH-specific imaging features were identified.

Types of interventions

Experimental interventions will be any permanent CSF shunting technique for the treatment of iNPH, including ventriculoperitoneal (VP) shunt, lumboperitoneal (LP) shunt, ventriculoatrial (VA) shunt, ventriculopleural (VPl) shunt, or third ventriculostomy.

Comparator interventions will be no CSF shunting, or the insertion of a shunt, but with the programmable valve not yet activated to a draining position (placebo shunt).

Types of outcome measures

Broadly, the outcome categories are:

- Gait function
- Cognitive function
- Urinary function
- Disability
- Quality of life
- Adverse events

We will assess non-adverse outcomes after CSF shunting in the short-term (less than six months), as we anticipate that there will be short-term control data. Due to the preferred cross-over trial design in the field of study, we anticipate that there will be no control data for long-term outcomes; we will provide descriptive analysis of any non-controlled long-term data available (longer than six months).

We consider gait function the primary efficacy outcome, along with disability and quality of life, because it is usually pivotal in the decision to conduct CSF shunting.

Primary outcomes

- Gait speed (short-term) – measured with validated global gait tools, e.g. the timed up and go (TUG) test, or 10-metre walk test (10MWT)
- Qualitative gait function (short-term) – measured with validated qualitative gait tools, e.g. the Tinetti score, or the Kubo NPH grading scale
- Patient disability (short-term) – measured with global disability scales, e.g. Modified Rankin Scale (mRS)
- Quality of Life (QoL; short-term) – measured with validated QoL scales
- Adverse events (short-term) – documented separately for serious complications and death. It is anticipated that this will be descriptive, as trials may define adverse events differently.
- Adverse events (long-term) – documented separately for serious complications and death. It is anticipated that this will be descriptive, as trials may define adverse events differently.

Secondary outcomes

- Gait speed (long-term) – measured with validated global gait tools, e.g. the TUG test, or the 10MWT
- Cognitive function (short-term) – measured with validated global cognitive screening tools, such as the Montreal Cognitive Assessment (MoCA), the Mini–Mental State Examination (MMSE), or the idiopathic normal-pressure hydrocephalus grading scale (iNPHGS (Hellström 2012))
- Qualitative cognitive function (short-term) – measured with validated scales (e.g. Keifer scale or Kubo iNPHGS)
- Cognitive function (long-term) – measured with validated global cognitive screening tools, such as the MoCA, MMSE, or iNPHGS (Hellström 2012)
- Urinary function (short-term) – measured with any appropriate scale

Search methods for identification of studies

Electronic searches

We will search ALOIS (alois.medsci.ox.ac.uk) - the Cochrane Dementia and Cognitive Improvement Group's Specialised Register. ALOIS is maintained by the Cochrane Dementia and Cognitive Improvement Group's Information Specialists, and contains dementia and cognitive improvement studies identified from the following:

- Monthly searches of a number of major healthcare databases: MEDLINE Ovid, Embase Ovid, CINAHL EBSCO, PsycINFO Ovid, and LILACS (Latin American and Caribbean Health Science Information database) BIREME
- Monthly searches of the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch)
- Monthly search of the Cochrane Library's Central Register of Controlled trials (CENTRAL)
- Six-monthly searches of ISI Web of Science Core Collection

We will run additional separate searches of: MEDLINE Ovid, Embase Ovid, CINAHL EBSCO, PsycINFO Ovid, Web of Science Core Collection (ISI Web of Science), ClinicalTrials.gov, and ICTRP to ensure we retrieve the most current results. The MEDLINE search strategy is in Appendix 1.

Searching other resources

We will review citation indices for the identified relevant articles

Data collection and analysis

Selection of studies

Two review authors will independently examine titles and abstracts of citations obtained from the searches, and exclude any clearly ineligible or duplicate articles, using Covidence (Covidence 2021). Following the initial screening, we will independently assess the full-text article for inclusion in the review, using pre-defined inclusion and exclusion criteria. A third review author will arbitrate disagreements, to create consensus. We will identify and record reasons for exclusion of the ineligible studies. We will record the selection process and create a PRISMA flow diagram (Moher 2009). The review authors will not be blind to trial authors, institution, or journal.

Data extraction and management

We will pilot the extraction process on at least one study in the review. We will use Covidence to manage study selection, and risk of bias assessment (Covidence 2021).

Two review authors will independently extract study characteristics and outcome data from included studies. Study characteristics will include: study design, setting, characteristics of participants (e.g. gender, age, ethnicity, disease severity, number of Hakim's triad of symptoms needed to fulfil NPH criteria for the study), randomisation, eligibility criteria, intervention details, type of control, the outcomes assessed, source of study funding, and investigator conflicts of interests. We will resolve disagreements by consensus, involving a third author (CC) where necessary.

For each outcome of interest, we will extract mean scores and standard deviations. When continuous outcome measures have been reported using different scales for the same construct, the lead review author (CC) will derive standardised mean differences, as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions,* Chapter 6.6.2.1 (Higgins 2021).

We will export data from Covidence to Review Manager Web software (RevMan Web 2022).

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias in studies, using the revised risk of bias in randomised trials (RoB 2) tool (Higgins 2021a; Sterne 2019). Any disagreements will be resolved by discussion with a third author to reach consensus agreement.

We will assess risk of bias for each study outcome, using the following Cochrane RoB 2 criteria:

- Bias arising from the randomisation process
- Bias due to deviations from intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

For each domain, we will answer a series of signalling questions with yes, probably yes, no information, probably no, or no, to determine the risk of bias (low risk, some concerns, and high risk). We will include text alongside the judgements to provide supporting information for our decisions.

We will decide the risk of bias for each outcome in our summary of findings tables (e.g. gait speed (short-term)) by its performance in each domain: if we judge one domain to have some concerns, we will take this judgement for the whole outcome. We will summarise the risk of bias in traffic lights on the forest plots.

Measures of treatment effect

We will calculate effect estimates with 95% confidence intervals (CIs), using time point scores for each trial outcome. If outcomes are measured with ordinal rating scales; provided these contained a reasonably large number of categories (more than 10), we will treat the data as continuous, arising from a normal distribution. When outcomes are measured with a single continuous scale, the measure of treatment effect will be the mean difference (MD). When the same outcome is measured on different scales, we will use a standardised mean difference (SMD). We will use 'Guiding rules' for interpreting SMDs (or Cohen's effect sizes), as outlined in Chapter 15.5.3.1 in the *Cochrane Handbook for Systematic Reviews of Interventions*, where a difference of 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect (Schünemann 2021a).

Unit of analysis issues

We anticipate that there will be several unit of analysis issues to contend with in this field of study:

One-arm cross-over trial design

There is a favoured one-arm cross-over trial design in iNPH, in which control participants are initially given inactive CSF shunts or no treatment (Saper 2017). At an early time point (usually three to four months), the control group is either shunted if they have not had a shunt, or the inactive shunts are turned to the active position. In this paradigm, there are no long-term controls, as all participants end the trial in the treatment intervention group. If, as anticipated, our search only detects trials of this design, we will have no long-term controlled trial data to use.

Therefore, in one-arm cross-over trials, we will compare short-term data between the intervention group (CSF shunt) and the control group (no shunt or inactive shunt), as for a parallel RCT design.

With a cross-over trial design, there will be groups of participants who have the control first (inactive shunt or no shunt), and then move into the treatment group, in which the CSF shunt is activated or they have a CSF shunt inserted. It is possible to analyse the effect of shunting in this group longitudinally (a pre-post, or before-and-after study design). These are non-randomised data, as the cases will always have the control first, followed by the active treatment intervention. We will not include these data in the main analysis, but will conduct an analysis to compare outcomes before and after shunting to see whether, and how results differ from the randomised parallel-groups dataset.

Outcomes

For some outcomes (e.g. qualitative gait function), we anticipate that we will encounter commonly applied, non-linear ordinal rating scales with few categories (e.g. Kubo Rating Scale). Without manipulating the original data, it will be impossible to binarise the individual scores into meaningful values. In this scenario, we will treat the data as continuous data, but will contextualise the effect size by referring to the original scale. When multiple different, but similar scales have been used, we will be unable to be specific about the effect-size.

We anticipate that there will be multiple measures of the same outcome. When this is the case, we will use the following principles to guide the selection of measures for data extraction, which are similar to those used by Bahar-Fuchs (Bahar-Fuchs 2019):

- We will use common and preferred outcome measures if reported by studies (e.g. TUG test or gait speed). When they are not available for a given study, we will use the most similar test reported.
- If multiple relevant scales are presented to measure the same outcome, we will consider creating a composite outcome score, as described in Bahar-Fuchs 2019.

Dealing with missing data

We will contact study investigators to obtain missing outcome or baseline characteristic data, when needed.

When the trials report change from baseline data only, we will compare this with time point data from the other studies identified in our search.

Assessment of heterogeneity

In addition to a visual inspection of the forest plots, we will assess statistical heterogeneity using a standard Chi^2 statistic and the associated I^2 statistic. Consistent with recommendations from Deeks 2021, we will deem heterogeneity to be present when the Chi^2 statistic is significant at the P = 0.1 level, or when I^2 suggests that more than 40% of the variability in the effect estimate is due to heterogeneity.

Assessment of reporting biases

We will assess in-trial reporting bias as part of our risk of bias assessment, by assessing whether outcomes reported in the methods section are reported in the results for the included studies. If our searches identify trial protocols, clinical trial registrations, or abstracts, indicating the existence of unpublished studies, we will attempt to determine the status of any unpublished studies by contacting the investigators.

Data synthesis

We will undertake meta-analysis using Review Manager Web when the results from more than one RCT are available, and we consider the trials sufficiently similar (RevMan Web 2022). We will use fixed-effect meta-analyses as we anticipate potential small-study effects, and we anticipate studies having very similar designs.

Subgroup analysis and investigation of heterogeneity

We anticipate identifying only a few studies, with relatively low sample sizes, and thus, do not intend to undertake subgroup analysis.

Sensitivity analysis

If we have sufficient studies, we plan to undertake these sensitivity analyses:

- remove studies with the highest risk of bias from the analysis for the major outcomes
- remove studies that used no-shunt comparator groups (as opposed to placebo-shunt comparator groups)
- remove studies in which the majority of participants had only one of the Hakim-Adam's triad of symptoms.
- If we consider that there may be important diversity between studies, we will re-run the analyses using a random-effects model, to test the robustness of findings with the meta-analytic model used.

Summary of findings and assessment of the certainty of the evidence

We will assess the certainty of evidence for each outcome, using the evidence grading system developed by the GRADE collaboration, as described in Chapter 14 of *Cochrane Handbook for Systemic Reviews of Interventions* (Schünemann 2021).

Two authors will independently apply the GRADE approach, and assess the certainty of evidence at high, moderate, low, or very low. We will discuss the certainty of evidence ratings for each outcome with the other members of the review team. A third review author will judge any disagreement, to reach consensus for final decisions on the ratings.

We will take the following factors into account when deciding whether or not to downgrade the certainty of evidence in relation to each outcome:

- Risk of bias
- Inconsistency of results
- Indirectness of evidence
- Imprecision of results
- Publication bias

Since we will only include RCTs, we will start with high certainty for each outcome. We will downgrade certainty of the evidence by one level if we consider there is a serious limitation in relation to a particular factor, or by two levels if we consider there to be a very serious limitation. We will explain our reason(s) for downgrading in the footnotes.

We will generate a summary of findings tables using GRADEpro GDT software (GRADEpro GDT). The summary of findings table will compare CSF shunt to no shunt or a placebo shunt (using randomised parallel-group data only) for the following outcomes;

- Gait speed (short-term)
- Qualitative gait function (short-term)
- Patient disability (short-term)
- Quality of life (QoL; short-term)
- Adverse events (short-term)
- Adverse events (long-term)
- Cognitive function (short-term)

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APPENDICES

Appendix 1. MEDLINE Ovid search strategy

1. exp Hydrocephalus, Normal Pressure/

2. normal pressure hydrocephalus.ti,ab.

3. NPH.ti,ab.

4. iNPH.ti,ab.

5. i-NPH.ti,ab.

6. or/1-5

7. exp Cerebrospinal Fluid Shunts/

8. shunt*.ti,ab.

9. or/7-8

10. randomized controlled trial.pt.

11. controlled clinical trial.pt.

12. randomized.ab.

13. placebo.ab.

14. drug therapy.fs.

15. randomly.ab.

16. trial.ab.

17. groups.ab.

18. or/10-17

19. exp animals/ not humans.sh.

20. 18 not 19

21. 6 and 9 and 20

CONTRIBUTIONS OF AUTHORS

Chris Carswell wrote the protocol. Chris Carswell, Anastasia Gontsarova, Kevin Tsang, Ron Pearce, Davina RIchardson, and Abi Methley all contributed to study design and subsequent manuscript editing.

DECLARATIONS OF INTEREST

The review team members declare no conflicts of interest.

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