TITLE: Efficacy of shunt surgery in normal pressure hydrocephalus: a randomized crossover study

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1. Abstract

Normal Pressure Hydrocephalus (NPH) is a treatable cause of dementia, gait apraxia and urinary incontinence that results in significant disability if not identified and treated. The pathogenesis of this disease is poorly understood it may involve ischemia damage caused by impaired cerebral blood flow following compression damage to the periventricular white matter. The shunting of CSF using ventriculoatrial (VA) or ventriculoperitoneal (VP) shunt is a commonly employed treatment of NPH. However, accurate diagnosis and selection of patients with shunt responsive NPH is critical for a favorable outcome following shunt surgery. The standard diagnostic tests for NPH such as clinical and radiological findings have proven to be less accurate than desired, with many patients remaining undiagnosed or untreated while others receive treatment due to a false-positive diagnosis. The response rates to shunting have been reported to vary between 31% to 89%. Furthermore, long term follow-up studies have shown loss of response to shunt which may be due to the natural history of disease, progression of comorbidities or a short term placebo effect following shunt surgery. The aims of this study are to determine (a) patient improvement in gait and other clinical measures in response to active shunt compared to placebo (non-active shunt) (b) predictors of response to shunt (c) long-term outcomes of patients with shunt (d) pilot assessment of sensitivity and specificity of commonly used scales to evaluate NPH. We propose a randomized double-blind cross-over study with a suboptimally draining/non-functioning shunt arm (equivalent of placebo) and an optimally draining/functioning shunt arm. Patients will be followed for 6 weeks on the first arm and then crossed over to the second arm and followed for an additional 6 weeks for the primary aim. Patients will then be followed for two years. Clinical outcomes include changes in gait, cognition, incontinence and functional independence.

2. Objectives (include all primary and secondary objectives)

Primary Outcome:
Changes in Gait

<u>Outcome Measure:</u>

Gait
Tinetti Tool
Timed Up and Go task (TUG**)**
MCV Gait Grade

Cognition

Mini Mental State Examination (MMSE)
Rey Auditory Verbal Learning Test (RAVLT)
Trail Making Test A & B
Writing the Alphabet
Beck Depression Inventory
Stroop test
Pegboard

Urinary

Urinary Incontinence Questionnaire (**ICIq-UI**)
Overactive Bladder Questionnaire (**ICIq-OAB**)
Quality-of-Life related to lower urinary tract symptoms (**ICIq-LUTSqol**)
Global quality-of-life assessment (**AUASSqol**)
Voiding diary

Functional Scales

Barthel Index
Modified Rankin Scale
SMAF Scale of Functional Autonomy

iNPH Scales

Kudo INPH grading Scale
Kiefer Index (Gait/balance, headache and dizziness domains)

Outcome Scales

Black Outcome Scale
Marmarou Recovery Scale
Post-Shunt Surgery Questionnaire

European NPH scale

Core imaging testing:

Sagittal MPRAGE
Axial T2
Axial FLAIR
Sagittal CISS midline
Sagittal phase contrast through the midline

Axial through plane cardiac gated phase contrast imaging aqueduct
DTI 30 directions 1 nex

Comorbidity Index

iNPH Diagnosis Checklist

3. Background

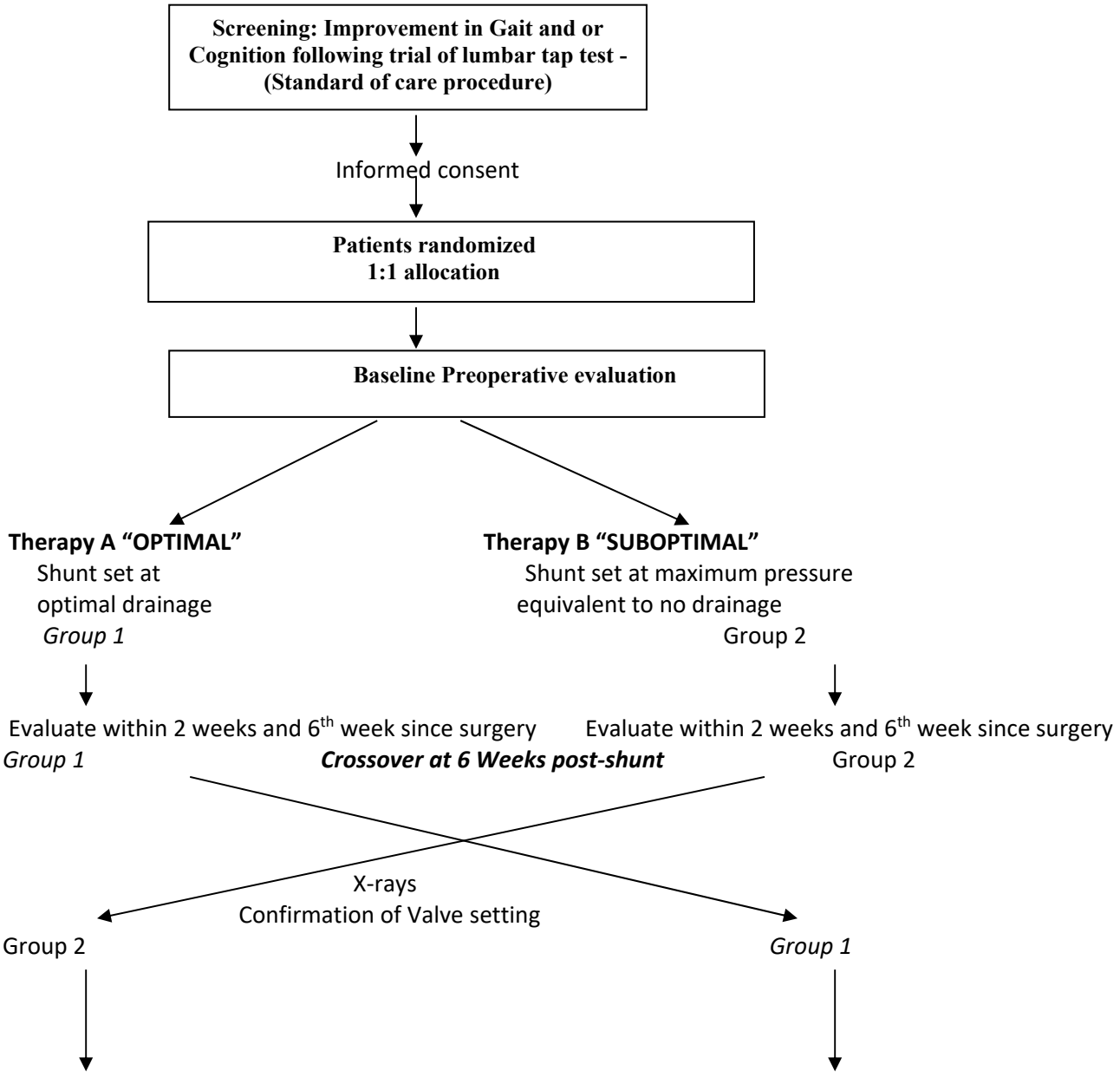
Normal Pressure Hydrocephalus (NPH) is a treatable cause of dementia, gait apraxia and urinary incontinence that results in significant disability if not identified and treated. The pathogenesis of this disease is poorly understood but may involve ischemia caused by impaired cerebral blood flow following strain in fibers of periventricular white matter. The standard diagnostic tests for NPH such as clinical and radiological findings have proven to be less accurate than desired, and many patients may remain undiagnosed and untreated. The symptoms of NPH are necessary but not sufficient to diagnose NPH and recommend shunt surgery. CT and MRI findings are not specific for NPH because they overlap with findings of cerebral atrophy or vascular dementia.

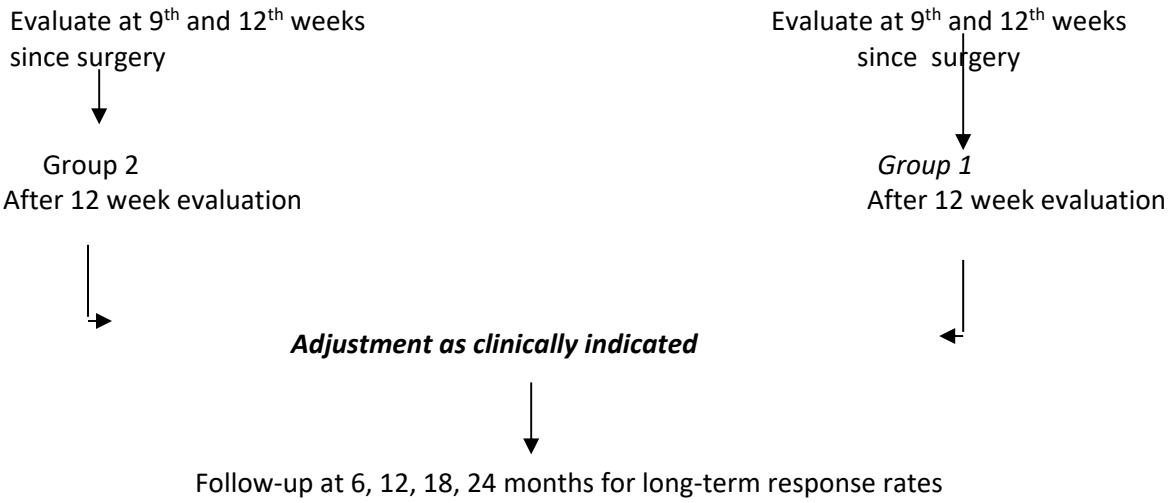
Although a shunt insertion improves NPH symptoms, response rates vary from 31% to 89%.[1-5] The largest published prospective series to date, that of Vanneste et al, enrolled 127 NPH patients and reported a 31% rate of improvement[6]. The Dutch NPH Study enrolled 95 patients with a 1year follow-up and observed a 64% rate of improvement[5]. Numerous other series with patients numbering between 25 and 45 have shown variable response rates ranging between 14% and 89% (most being less than 50%) with follow-up typically one year or less[4]. A recent meta-analysis of all series reported in the literature by Hebb et al. found a combined long-term response rate of 29% to CSF shunting[4]. Our preliminary studies have shown that objective physiological measurements of gait and cognitive assessment can demonstrate improvement after shunt[3,7-9]. Raftopoulos et al, using a wide battery of tests, described improvement in 67% of 21 patients within a 12-month follow-up period[10]. However, Savolainen et al found no significant difference in memory disturbances after shunting[11]. McGirt et al, demonstrated a long term improvement rate of 75% after shunting 132 patients with NPH[8]. Duinkerke et al. reported significant improvement in 6 out of 10 patients (60%) over a 6-12 month follow-up period[9]. Thus, despite a vast body of evidence regarding the efficacy of shunt in Normal Pressure Hydrocephalus the response rates remain inconclusive and vary widely. We believe that this problem of variable response is due to lack of universally accepted identification criteria to select patients for shunt surgery and a strong placebo effect which prevails following placement of shunt. We thus propose a randomized, double blind, placebo controlled crossover study designed to assess improvement in gait, incontinence and cognition and to validate our selection criteria . In addition, the study aims to identify scales/ instruments of measurement which are most

sensitive and specific to progression or improvement in clinical status of the patient. We will therefore correlate scores on the Comorbidity Index, Kubo INPH Scale, Kiefer's index domains for gait/balance, headache and dizziness, European NPH Scale, INPH Diagnosis Checklist with the Black Outcome Scale, Marmarou Recovery Scale , modified Rankin scale, Barthel index. Furthermore, we would test the hypothesis of association of NPH with congenital hydrocephalus or early childhood changes in brain (long standing overt ventriculomegaly) which may manifest as large heads. We will correlate head circumference at baseline and with outcomes at various time points.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures
(Distinguish research procedures from those that are part of routine care).





The study is a randomized 2x2 double-blinded cross-over design study with two arms- comparing optimally functioning shunts (Optimal drainage) to the placebo treatment wherein there is minimal CSF flow through the shunts (sub-optimal drainage). The state of sub-optimal drainage of shunt will be attained by raising the opening pressure of the shunt valve to maximum which will impede the CSF flow. All patients who are candidates for shunt surgery based upon standard of care practice of CSF drainage trial will enter the study. Only patients who are not at significant risk of falls will be included in the study i.e patients with Tinetti score >18. Furthermore, the neurosurgeon/neurologist will not be blinded to patients shunt valve status. Only the nurse practioner or physiotherapist performing the study evaluation would be blinded. All evaluation data would be made available to neurologist/ neurosurgeon remain informed about treatment failure (Tinetti Gait and evaluation≤18).

During the initial phase of the study, participants will be randomized in 1:1 allocation ratio to optimally and sub-optimally draining shunt arms. After completion of six weeks the opening pressures for patients in the optimally draining shunt arm will be raised to minimize CSF flow (crossover to sub-optimally draining arm). Likewise, at 6 weeks patients initially in suboptimal drainage arm will have the opening pressures appropriately reduced so that flow through the shunt is optimal (crossover to optimal drainage shunt arm). X-rays will be performed to confirm shunt valve settings. Since the shunt is only effective during the time it is effectively draining and the carryover effect is minimal (i.e., often lasting for no more than a few days), there will be no washout period between arms. Patients will undergo every third week evaluations regardless of the study arm to evaluate safety as well as efficacy. Patients and the psychometrician, physical therapist and nurse practitioner who assess the outcome measures will be blinded to the shunt status. Only the study neurosurgeon and neurologist will be aware of the shunt status, and will make clinical (safety) decisions after being informed of Tinetti gait and balance scores. The follow-up and evaluation timeline is indicated in the algorithm above. The Neurosurgeon will be notified about the gait and balances score and will make a clinical (safety) decision accordingly. Any patient whose gait deteriorates to Tinetti ≤ 18 or has a fall will be regarded as a treatment failure. Patients who are a treatment failure during the

suboptimal drainage arm will have the opening pressure of the valve adjusted. These patients would then be considered to be crossed over to draining arm if they were in the initial sub-optimal drainage arm of the study. If a patient who has already been crossed over from optimally draining shunt to sub-optimally draining shunt arm worsens, s/he will have the shunt pressure turned down and will be followed according to standard of care protocol at 6 monthly intervals. During this time, we will collect data on these follow-up visits as part of the research.

Standard of care procedures: Shunt surgery, Post op evaluations while shunt is in optimal drainage setting, 6, 12 months, 18 months and 24 months post-op visit

Research procedures: Visits during non-draining shunt period

b. Study duration and number of study visits required of research participants.
The study duration and number of visits for each participant will vary depending on the arm of the study the patient enters first (flow chart above).
Non-Draining➔Draining Shunt arm
Baseline preoperative visit ➔Shunt surgery➔ Sub-optimally draining shunt➔ first visit within 2 weeks from surgery 6 weeks visit, ➔cross over to draining Shunt arm at 6 week visit along with x-rays confirmation of the new valve settings➔9 weeks visit➔12 weeks visit
Total duration 12 weeks from shunt surgery
Number of total Visits=4

Draining➔Non-Draining Shunt arm
Baseline preoperative visit ➔Shunt surgery➔ Draining shunt➔ first visit within 2 weeks from first surgery ➔, 6 weeks visit, ➔cross over to non-draining Shunt arm at 6 week visit along with x-rays confirmation of the new valve settings ➔ 9 weeks visit➔12 weeks visit
Total duration 12 weeks from shunt surgery
Number of total Visits=4

c. Blinding, including justification for blinding or not blinding the trial, if applicable.
Patients and raters will be blinded to treatment status to minimize reporting bias. Neurologist and neurosurgeons will not be blinded for safety reasons.

d. Justification of why participants will not receive routine care or will have current therapy stopped.
The study is designed to compare efficacy of shunt in comparison to sham/placebo (non draining shunt). Though shunt is standard of care it has not been systematically evaluated in a randomized trial. The length of time that a patient will have a non-draining shunt has been limited to 6 weeks and will be shortened if the patient shows a worsening in gait while on that arm.

e. Justification for inclusion of a placebo or non-treatment group.
The placebo arm is included to take into account any placebo effect. Current standard of care treatment of normal pressure hydrocephalus has not been evaluated in a placebo controlled trial. Current guidelines are based on studies which lack a comparison with placebo and their

outcomes have been highly variable. Thus a placebo control is needed to evaluate efficacy of shunt and to improve our selection criteria for shunt insertion.

f. Definition of treatment failure or participant removal criteria.

1. Failure: Any participant whose gait deteriorates to Tinetti≤18 will be considered a treatment failure as this is considered under standard of care to be high risk of fall. Additionally any patient falling due to inability to balance or poor gait would also be considered a treatment failure.
   Any patient deteriorating to failure level or having a fall attributable to gait impairment will be recorded as a treatment failure for that arm of the study and if on suboptimal drainage arm will be crossed over to optimal drainage level.

   Patients who fail would however continue to participate in study and data will be collected at all subsequent follow-up points regardless of the study arm as described above. Furthermore, for concerns of patient safety no patient who fails (Tinetti ≤ 18) will subsequently have suboptimal drainage in shunt at anytime[12,13].

Response:

Gait

1. Tinetti gait and balance scale: Measured with respect to baseline (pre-drainage trial scores)

2. TUG: Measured with respect to baseline (pre-drainage trial scores)

3. MCV Gait Grade: Measured with respect to baseline (pre-drainage trial scores)

Cognition

1. Mini Mental State Examination (MMSE)

2. Rey Auditory Verbal Learning Test (RAVLT): Measured with respect to baseline (pre-drainage trial scores)

3. Trail Making Test A & B : Measured with respect to baseline (pre-drainage trial scores)

4. Writing the Alphabet : Measured with respect to baseline (pre-drainage trial scores)

5. Beck Depression Inventory

6. Stroop test

7. Pegboard

Urinary

1. Urinary Incontinence Questionnaire (**ICIq-UI**) : Measured with respect to baseline (pre-drainage trial scores)

2. Overactive Bladder Questionnaire (**ICIq-OAB**) : Measured with respect to baseline (pre-drainage trial scores)

3. Quality-of-Life related to lower urinary tract symptoms (**ICIq-LUTSqol**) : Measured with respect to baseline (pre-drainage trial scores)

4. Global quality-of-life assessment (**AUASSqol**) : Measured with respect to baseline (pre-drainage trial scores)

5. Voiding Diary

Functional Scales

1. Barthel Index: measured with respect to baseline (pre-drainage trial scores)

2. Modified Rankin Scale

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

5. Inclusion/Exclusion Criteria

3.1 Inclusion Criteria

- Age of Patients (between 55 to 85 years old)
- Clinically suspected iNPH with at least gait impairment.
- Ventriculomegaly defined by CT or MRI, Evans' index > 0.3

- Clinical improvement after - 50 cc lumbar tap test.
- MMSE≥ 14
- Patients with Tinetti gait and balance score>18
- Kiefer Comorbidity index<5
- Informed consent from patient

3.2 Exclusion Criteria

- Etiology for hydrocephalus other than idiopathic normal pressure hydrocephalus
- MMSE<14
- Patients who have Tinetti gait and balance scores of ≤18
- Kiefer Comorbidity index>5
- Patients not capable of providing an informed consent.
- History of intra-cerebral hemorrhage

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.
CSF diversion using shunt surgery is the standard of care treatment for the normal pressure hydrocephalus

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.
n/a

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

d. n/a

7. Study Statistics

a. Primary outcome variable.
The primary short term outcome variable will be the Tinetti gait and balance score, the MCV Gait Grade and the gait velocity defined as number of steps per second per 30 feet walk at 6 and 12 weeks after surgery.

The primary long term outcome variable will be the Tinetti gait and balance score, the MCV Gait Grade and the gait velocity defined as number of steps per second per 30 feet walk at 6 and 12 months after surgery.

b. Secondary outcome measures.
Secondary outcome measures include the - cognitive and incontinence measures, the Black Outcome Scale, the Marmarou Recovery Scale , the functional measures of the Barthel index,

SMAF Scale and Rankin Scale, Post-Surgery Questionnaire, Kudo iNPH grading scale, Kiefer Index and European NPH Scale.

Also, outcome measures at earlier time points (i.e., the first visit 2 weeks from surgery - and 6-week follow-up) will be examined as well as the slope of the change in the measures over the follow-up.

c. Statistical plan including sample size justification and interim data analysis.

General analytic method:
For each treatment order group, we will calculate the within patient paired differences of the 6 and 12 week follow-up measures. We will examine the distributions of these summary measures, and if not normally distributed, log transformation will be tried. If near normality cannot be achieved then non-parametric analyses will be used.

Though we do not expect any carryover effects, we will first test for period effects and treatment-period interactions by testing whether the magnitudes of the mean period differences are unequal and whether the overall means for each treatment order group are different. General linear models will be used to assess treatment effect while accounting for within patient correlation. F-tests (or non-parametric Wilcoxon rank sum tests if normality cannot be achieved) will be used to test significance of treatment effects.

Specifically for the primary outcome:
We will calculate the within patient difference in the Tinetti gait score , the MCV Gait Grade and the gait velocity at 6 weeks (end of first treatment period) and at 12 weeks (end of second treatment period). This difference is the same as it would be if we calculated the change from baseline at each time period. General linear model analysis will be employed to test for period and treatment effects and the interaction, while accounting for within patient correlation. If there is no period effect, then the analysis can be simplified to reporting a paired t-test of the difference in the Tinetti gait score , the MCV Gait Grade and the gait velocity between the optimal and sub-suboptimal 6-week follow-up. If any patient is a treatment failure and is discontinued from a treatment arm, the measure at the time of failure will be carried forward to the 6-week measure.

Sample size calculation:
A mean difference in the Tinetti score of 5 points would be considered clinically meaningful. Given the inclusion criteria of a baseline Tinetti score of >18 and data from our clinic, we estimate the standard deviation for the change to be 5 points. Using a two-sided t-test with the Type I error level of 0.05, we will have 80% power to reject the null hypothesis of no difference when the total sample size of a 2x2 crossover design is 34. Adjusting for a dropout rate of 20% a sample size of 42 study subjects would be required.

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