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Shunting outcomes in communicating hydrocephalus: A multi-center, open-label, randomized controlled trial

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Abstract

Introduction: Ventriculoperitoneal shunt (VPS) remains the most widely utilized methods to treat communicating hydrocephalus. More recently, lumboperitoneal shunt (LPS) has been suggested as a reasonable option in some studies. However, there is lack of high-quality studies comparing these two techniques in order to certain the benefits and harms to utilize one of these 2 methods. The purpose of the current study is to determine the effectiveness and safety of the LPS versus the VPS in patients with communicating hydrocephalus.

Methods and analysis: All eligible patients aged 18-90 years with communicating hydrocephalus will be recruited and then randomly allocated into LPS or VPS group in a ratio of 1:1. All patients will be analyzed before shunt insertion, on the day of discharge, 1 month, 6 months, 12 months and 24 months postoperatively. The primary outcome measure is the rate of shunt failure at 2-year follow-up term. The secondary outcomes include Keifer's Hydrocephalus Scale (KHS), National Institute of Health stroke scale (NIHSS), Glasgow Outcome Scale Extended (GOS-E), Evans index, safety endpoints, and cost-effectiveness of hospital stay.

Ethic and dissemination: The study will be performed in compliance with the Declaration of Helsinki (2002) of the World Medical Association. The study was approved by Institutional Review Board of West China Hospital and registered through Chinese Clinical Trial Registry (ChiCTR) in March 2021. All patients will be fully informed the potential benefits, potential risks, and responsibilities, those who will sign the informed consents once they are included. Preliminary and final results will be published in peer-reviewed journals and presented at national and international congresses.

Trial registration number: ChiCTR2100043839; Pre-results.

Strengths and limitations of this study

1. This study is the first randomized controlled trial about comparing the two most popular surgical methods in the treatment of communicating hydrocephalus.
2. The current study will provide to provide high-level evidence on the benefits and harms to use one of these 2 methods
3. This study will provide the evidence on the indications and contraindications to perform shunt, the standard procedures, and the optimal option.
4. This trial will also help to help to create an algorithm for the selection of suitable patients, pre-shunt and post-shunt management.
5. Medical condition and experience of attending surgeons are various.

Introduction

Communicating hydrocephalus, a common type of hydrocephalus, is pathological process where ventricles enlarged, progressively compressing periventricular white matter.[1-3] Intracerebral hemorrhage (ICH) is one of common risk factors for communicating hydrocephalus, along with traumatic brain injury (TBI) and intracranial infection.[4,5] Some elderly population to develop communicating hydrocephalus without any known causes are historically diagnosed as idiopathic normal-pressure hydrocephalus (INPH).[6]

Different strategies for diverting cerebrospinal fluid (CSF) have long been proposed as standard treatments for communicating hydrocephalus. Ventriculoperitoneal shunt (VPS) remains the most widely utilized methods to treat communicating hydrocephalus.[7] More recently, lumboperitoneal shunt (LPS) has been suggested as a reasonable option in some studies, though this is typically recommended when patients are diagnosed as INPH.[8] For instance, LPS has become the superior option for patients with INPH over VPS in Japan. Some clinical trials also indicated LPS was safe and effective for other types of communicating hydrocephalus including post-hemorrhagic hydrocephalus (PHH) and post-traumatic hydrocephalus (PTH).[9-13]

LPS has some advantages over VPS, including the avoidance of brain injury and lower incidence of infection.[14] Despite potential advantages, whether LPS is the optimal option in patients with communicating hydrocephalus is unclear. Currently, there are no randomized studies comparing the efficacy of these 2 techniques. The Early evidence had ever revealed LPS was more likely to undergo shunt failure compared with VPS while a recent retrospective study suggested equivalent clinical results of LPS and VPS in patients with PHH.[11,15] In addition, Giordan et. al[16] recently performed a systematic review and meta-analysis, suggesting the shunting outcomes did not differ significantly among different CSF diversion techniques used. However, there is lack of high-quality studies comparing these two techniques in order to certain the benefits and harms to use one of these 2 methods. The purpose of the current study is to determine the effectiveness and safety of the LPS versus the VPS in patients with communicating

hydrocephalus.

Objective

The purpose of the current study is to determine the effectiveness and safety of the LPS versus the VPS in patients with communicating hydrocephalus.

Methods and analysis

Patient and public involvement

No patient or public is involved in study design, recruitment or conduct of the study.

Study design and settings

The current study is a multi-center, open-label, and randomized controlled trial in which 550 patients with communicating hydrocephalus will be randomly allocated into LPS or LPS group in a ratio of 1:1. Patients will be enrolled at 20 neurosurgical centers in China Mainland that are experienced and skilled in both neurosurgery and shunt surgery. Each participating site will receive the local ethics committee approval, or obey our ethics committee review decision. We will propose the standardized procedures for CSF diversion and perioperative management before enrollment, and every attending neurosurgeon will be trained centrally. All patients will be fully informed the potential benefits, potential risks, and responsibilities, those who will sign the informed consents once they are included. This study protocol is developed following the Guidelines of Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).[17]

Sample size

A recent meta-analysis indicated the rate of VPS failure and LPS failure were 18.0% and 14.0%, respectively.[18] In this light, a sample of 250 for each group will be required in this trial while the significance level (two-sided) is 5% and the test power is 80%. Considering about the loss to follow-up, the sample size is enlarged to 275 for each group.

Recruitment and eligibility criteria

Figure 1 shows the flow-chart of the selection of patient. The enrollment is expected to commenced in Jul 2021 and end in Dec 2025. Participants are recruited on outpatient department. Each participant will receive financial compensation. Specifically, once

the eligible participants are admitted, 3-dimension brain and spine magnetic resonance imaging (MRI) scan will be performed to further evaluate the ventricles, aqueduct, basal cisterns, and spinal subarachnoid space, as well as to calculate the Evans index. Additionally, lumbar drainage is required to determine the eligibility.

Inclusion criteria

1. Age 18-90 years;
2. Non-obstructive hydrocephalus;
3. Evans index > 0.3;
4. The communication of the ventricles with lumbar subarachnoid space is evident through lumbar puncture and CSF opening pressure is 70-200 mmH_2O

Exclusion criteria

1. Obstructive hydrocephalus;
2. Negative-pressure hydrocephalus;
3. Chiari malformation;
4. Prior history of shunt;
5. Lumbar fracture;
6. Decline to lumbar puncture.

Randomization and blinding

Subjects who meet the inclusion criteria and sign the informed consents will be randomly allocated into one of two groups in a ratio of 1:1. The randomized allocation using a random number table will be conducted by a designated member who will not involve in other activities of study patients. The randomization is not likely to blind for the subjects or attending neurosurgeons, but it is secret for the data collectors, investigators, and analysts.

Intervention

Neurosurgeons with extensive experience in the different procedures of CSF diversions will perform VPS or LPS, and will be trained centrally in advance and reach uniform standard. We will use the shunt system with programmable pressure valve, obtained from Medtronic (USA) or Sophysa (France). No matter which types of shunt system

utilized, the initial pressure for the shunt system will set to the highest level before surgery.[19] Shunt function is checked when there is no improvement in clinical symptoms is observed.[20] The pressure setting will be lowered by 1 step with careful consideration of the patient's safety at the time when symptoms are not improve after the operation.

VPS

VPS implantation is performed under general anesthesia and the patients are positioned in the supine position with the head turned to the left. Access to the lateral ventricle is obtained through frontal scalp incision, skull drilling, and dura incision. Peritoneal access is obtained via a minimal invasive incision or split trocar access. A subcutaneous tunneler is passed from the abdominal incision to the cranial incision. The valve is placed at the cranial incision with a 3-point fixation to the subcutaneous tissue. Once the cranial catheter is connected to the valve and the valve is connected to the peritoneal tubing with confirmation of adequate CSF flow, the peritoneal catheter is inserted into the peritoneal space.

LPS

LPS implantation is performed under general anesthesia and the patients are positioned in the lateral position. A lumbar catheter is inserted through the L3/4 or L2/3 interlaminar space into the spinal subarachnoid space. The catheter is then placed in a subcutaneous pocket made at the flank region. Peritoneal access is obtained via a minimal invasive incision or split trocar access. A tunneler is passed from the abdominal incision to the flank region, and then to the lumbar incision. The valve is placed at the frank region with a 3-point fixation to the subcutaneous tissue. Once the lumbar catheter is connected to the valve and the valve is connected to the peritoneal tubing with confirmation of adequate CSF flow, the peritoneal catheter is inserted into the peritoneal space.

Outcomes

Based on the study schedule (Table 1), all patients will be analyzed before shunt insertion, on the day of discharge, 1 month, 6 months, 12 months and 24 months

postoperatively.

Primary outcome

The primary outcome measure is the rate of shunt failure at 2-year follow-up term. On the basis of previous studies, shunt failure is defined as the occurrence of shunt revision owing to shunt obstruction, breakage, tubing exposure, malfunction, disconnection, infection, or other conditions that require shunt revision. Shunt failure is also considered if improvement of symptoms or neurological function is not observed. Shunt success is defined as the absence of shunt failure.

Secondary outcome

The secondary outcomes include Kiefer's Hydrocephalus Scale (KHS), National Institute of Health stroke scale (NIHSS), Glasgow Outcome Scale Extended (GOS-E), Evans index, and safety endpoints, within 2 years after shunt implantation, as well as the cost-effectiveness of hospital stay. KHS, a scale proposed by Kiefer[21], consists of five items: gait disturbances, mental disorder, urinary incontinence, headache, and vertigo. The score of KHS ranges from 0 to 25 (higher is worse). The improvement of neurological function is evaluated by NHISS. A positive response to shunt implantation will be defined as an improvement of more than 1 point in the KHS or NIHSS at evaluation point. Evans index is calculated by the axial brain magnetic resonance imaging (MRI) scan.

Safety endpoint include surgical complications, any adverse events, and length of stay. Severe adverse events (SAEs) refer to death, life-threatening events, shunt-related disability, hospitalization for emergencies or intensive care unit, or an prolonged hospitalization period.

The cost-effectiveness of hospital stay will synchronously be investigated since the implanted system is not similar and the postoperative cost will be associated to the occurrence and management of complications.

Data collection and management

All patients will be analyzed before shunt insertion, on the day of discharge, 1 month, 6 months, 12 months and 24 months postoperatively. At each site, 2 independent

investigators will collect the baseline data such as age, gender, etiology, date of admission, comorbidities, Glasgow Coma Scale (GCS), symptoms, KHS, NIHSS, Evans index, CSF parameters, and CSF opening pressure. All patients will be follow-up on a regular basis by outpatient visits. All data from hospitalization and follow-up visits will be recorded in a paper-based table and then fixed into an electronic database. All data will be carefully examined and verified by these 2 investigators.

Statistical analysis

All data will be analyzed using the statistical software program SPSS version 19 (IBM, Armonk, New York). Probability values (*P*) less than 0.05 is considered to have statistical difference. Categorical variables are statistically descried as number (percent). We will use Chi-square test to compare the difference on categorical variables (Fisher's exact test is used while appropriate). As referring to quantitative data, we will use Kolmogorov-Smirnov test is to determine the normality. If quantitative data follows normal-distribution, described as arithmetic mean ± standard deviation (SD), we will use *t*-test to compare the difference. Other quantitative data will be described as median (range) and we will use Wilcoxon rank sum test to compare the difference. Shunt-success rate curve is obtained using the method of Kaplan-Meier and log-rank test is used to compare the difference between the 2 groups.

Data and safety monitoring

We will set up a data monitoring committee (DMC) guarantee the safety of this trial. All SAEs will be recorded in detail and reported to ethics committee. Members of the DMC will review all adverse events regularly, and hold a seminar to assess the risk of the study if necessary.

Data available statement

The datasets generated and analyzed during the current study are available from Research Manager (http://www.medresman.org.cn.), as well as the corresponding author on reasonable request.

Discussion

This study is currently the first randomized controlled trial comparing the two most

popular surgical techniques of shunt surgery (LPS and VPS) in the treatment of communicating hydrocephalus in order to provide high-level evidence. We believe that this trial is necessary since the benefits and harms to utilize one of these 2 methods are poorly understood. The results of the current study could be the evidence for shunt-dependent hydrocephalus guidelines: the indications and contraindications to perform shunt, the standard procedures, and the optimal option. This trial will also help to help to create an algorithm for the selection of suitable patients, pre-shunt and post-shunt management.

Despite the potential strengths, there are some aspects of issues that need to be discussed. First, KHS is chosen to evaluate the improvement of symptoms in this trial. Currently, there are no commonly accepted scales with the respect to the evaluation of symptoms for communicating hydrocephalus. However, there are a number of clinical scales widely used in patients with INPH such as INPH grading scale (INPHGS) and Mini-Mental State Examination (MMSE), which are focusing on the typical syndrome of INPH (gait/balance disturbance, dementia, urinary incontinence).[22] Patients with communicating hydrocephalus are possible to develop various symptoms and signs. In this regard, KHS is a more appropriate scale since the five items of KHS are common symptoms for communicating hydrocephalus.[10,21] Besides, the combination of KHS with NIHSS in this trial are probably superior to accurately evaluate the neurological symptoms and function.

Second, in terms of CSF opening pressure, we believe that pressures that are dramatically higher or lower than a range are likely not suitable for the upcoming LPS surgery. According to the Western guideline for the diagnosis of INPH,[23] CSF opening pressure in the range of 70-245 mm H_2O is consistent with a probable NPH diagnosis but the range is suggested to be <200 mm H_2O based on the Japanese guidelines for the diagnosis of INPH.[24] In addition, there is no consensus in the optimal CSF opening pressure to perform LPS implantation. Taken together, a range of 70–200 mm H_2O is chosen in this study.

Ethic and dissemination

The study will be performed in compliance with the Declaration of Helsinki (2002) of the World Medical Association. The study was approved by Institutional Review Board of West China Hospital and registered through Chinese Clinical Trial Registry (ChiCTR) in March 2021. All patients will be fully informed the potential benefits, potential risks, and responsibilities, those who will sign the informed consents once they are included. Preliminary and final results will be published in peer-reviewed journals and presented at national and international congresses.

Authors' contributions

TS contributed to conceptualization, methodology, quality assessment, and writing original draft. WC and JY contributed to data curation, software, and formal analysis. YK and YZ contributed to investigation. PL and HY contributed to formal analysis and writing original draft. CY contributed to conceptualization, quality assessment, and manuscript revision. JW contributed to conceptualization, quality assessment, supervision, funding acquisition, and manuscript revision. All authors approved the final manuscript.

Funding statement

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Competing interests

None declared.

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Figure 1 Flow chart of the selection pf patients. VPS, ventriculoperitoneal shunt; LPS, lumboperitoneal shunt; CSF, cerebrospinal fluid; Keifer's Hydrocephalus Scale;

NIHSS, National Institute of Health stroke scale; GOS-E, Glasgow Outcome Scale Extended.

Table 1 Study schedule

	Baseline	Discharge	1 month	12 months	24 months
KHS	√	√	√	√	√
NIHSS	√	√	√	√	√
GOS-E	√	√	√	√	√
Evans index	√	√	√	√	√
Shunt outcome†		√	√	√	√
Complications		√	√	√	√
Mortality		√	√	√	√
Cost-effectiveness		√			

Evans index will be calculated through the magnetic resonance imaging (MRI) scan.
† "Shunt outcome" includes shunt failure and shunt success.
KHS, Keifer's Hydrocephalus Scale; NIHSS, National Institute of Health stroke scale; GOS-E, Glasgow Outcome Scale Extended.

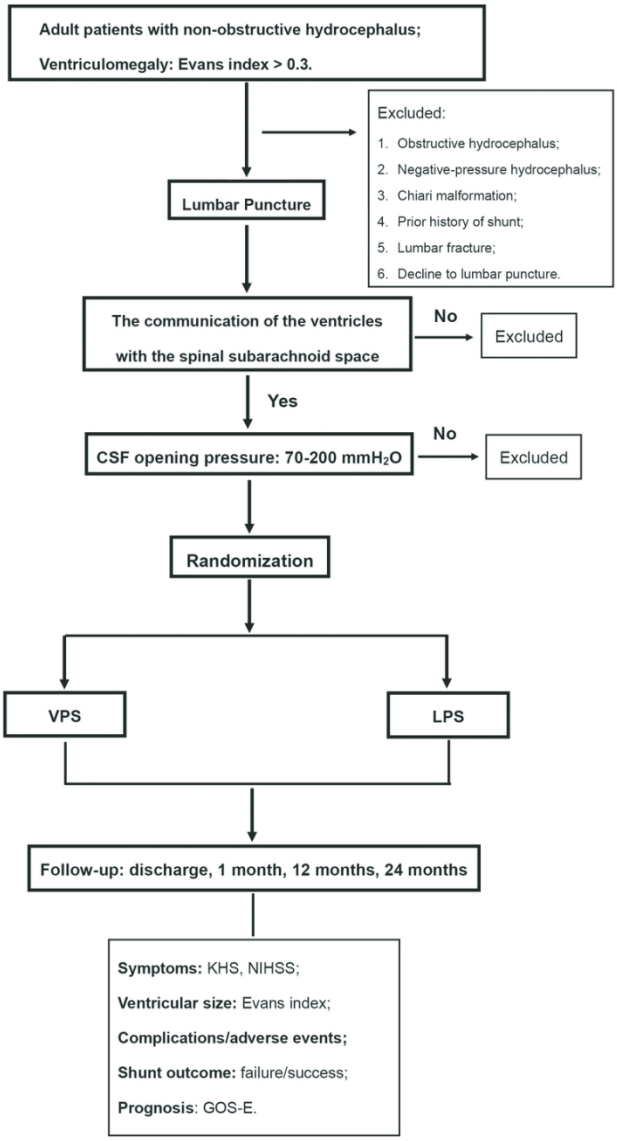

Figure 1. Flow chart of the selection pf patients. VPS, ventriculoperitoneal shunt; LPS, lumboperitoneal shunt; CSF, cerebrospinal fluid; Keifer's Hydrocephalus Scale; NIHSS, National Institute of Health stroke scale; GOS-E, Glasgow Outcome Scale Extended.

71x128mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 2
	2b	All items from the World Health Organization Trial Registration Data Set	Page 2
Protocol version	3	Date and version identifier	-
Funding	4	Sources and types of financial, material, and other support	Page 11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 1 and 11
	5b	Name and contact information for the trial sponsor	-
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	-
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Page 5 and 9
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 4
	6b	Explanation for choice of comparators	Page 4
Objectives	7	Specific objectives or hypotheses	Page 5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 5 and 6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 6 and 7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page 6 and 7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 6 and 7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 6 and 7

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 7 and 8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 7, Table 1, and Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 5
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 6
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 8 and 9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 9
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 9
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page 9
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 9

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 9
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Page 11
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 8 and 11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 11
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 11
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Page 11
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Shunting outcomes in communicating hydrocephalus: Protocol for a multi-center, open-label, randomized controlled trial

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Shunting outcomes in communicating hydrocephalus: Protocol for a multi-center, open-label, randomized controlled trial

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Abstract

Introduction: Ventriculoperitoneal shunt (VPS) remains the most widely utilized methods to treat communicating hydrocephalus. More recently, lumboperitoneal shunt (LPS) has been suggested as a reasonable option in some studies. However, there is lack of high-quality studies comparing these 2 techniques in order to certain the benefits and harms to utilize one of these 2 methods. The purpose of the current study is to determine the effectiveness and safety of the LPS versus the VPS in patients with communicating hydrocephalus.

Methods and analysis: All eligible patients aged 18-90 years with communicating hydrocephalus will be recruited and then randomly allocated into LPS or VPS group in a ratio of 1:1. All patients will be analyzed before shunt insertion, at the time of discharge, 1 month, 6 months, 12 months and 24 months postoperatively. The primary outcome measure is the rate of shunt failure at 2-year follow-up term. The secondary outcomes include Keifer's Hydrocephalus Scale (KHS), National Institute of Health stroke scale (NIHSS), Glasgow Outcome Scale Extended (GOS-E), Evans index, safety endpoints, and cost-effectiveness of hospital stay.

Ethics and dissemination: The study will be performed in compliance with the Declaration of Helsinki (2002) of the World Medical Association. The study was approved by Institutional Review Board of West China Hospital and registered through Chinese Clinical Trial Registry (ChiCTR) in March 2021. All patients will be fully informed the potential benefits, potential risks, and responsibilities, those who will sign the informed consents once they are included. Preliminary and final results will be published in peer-reviewed journals and presented at national and international congresses.

Trial registration number: ChiCTR2100043839; Pre-results.

Strengths and limitations of this study

1. This study is the first randomized controlled trial about comparing these two procedures of CSF diversions in the treatment of communicating hydrocephalus.
2. The current study will provide high-level evidence on the advantages and disadvantages of these 2 methods
3. This study will provide high-level evidence on the optimal option in the treatment of normal-pressure hydrocephalus based on a randomized controlled trial.
4. This trial will help to create an algorithm for the selection of suitable patients, pre-shunt and post-shunt management.
5. Medical condition and experience of attending surgeons are sometimes various leading to potential bias but the neurosurgeons will be trained centrally in advance and reach uniform standard.

Introduction

Communicating hydrocephalus, a common type of hydrocephalus, is the pathological process where ventricles enlarged, progressively compressing periventricular white matter.[1-3] Intracerebral hemorrhage (ICH) is one of common risk factors for communicating hydrocephalus, along with traumatic brain injury (TBI) and intracranial infection.[4,5] Some elderly population to develop communicating hydrocephalus without any known causes are probably diagnosed as idiopathic normal-pressure hydrocephalus (INPH).[6]

Different strategies for diverting cerebrospinal fluid (CSF) have long been proposed as standard treatments for communicating hydrocephalus. Ventriculoperitoneal shunt (VPS) remains the most widely utilized method to treat communicating hydrocephalus.[7] Endoscopic third ventriculostomy (ETV) is an alternative and effective option for obstructive hydrocephalus, and has recently been performed for communicating types of hydrocephalus.[4,8,9] A randomized controlled trial showed patients with INPH treated by ETV obtained worse neurological outcomes and higher incidence of severe complications than those who were treated with VPS.[10] More recently, lumboperitoneal shunt (LPS) has been suggested as a reasonable option in some studies, though this is typically recommended when patients are diagnosed as INPH.[11] For instance, LPS has become the superior option for patients with INPH over VPS in Japan. Some clinical trials also indicated LPS was safe and effective for other types of communicating hydrocephalus including post-hemorrhagic hydrocephalus (PHH) and post-traumatic hydrocephalus (PTH).[12-16]

LPS has some advantages over VPS, including the lower risk of brain injury and lower incidence of infection.[17] Despite potential advantages, the comparison of VPS to LPS in the treatment of communicating hydrocephalus is poorly understood. Currently, there are few prospective studies comparing the efficacy of these 2 techniques. Early evidence had ever revealed LPS was more likely to undergo shunt failure compared with VPS (7% vs 1%) while a recent retrospective study suggested patients with communicating hydrocephalus secondary to ICH treated by VPS or LPS had equivalent

clinical results.[14,18] In addition, Giordan et. al[19] recently performed a systematic review and meta-analysis, suggesting the shunting outcomes did not differ significantly among different CSF diversion techniques used. However, there is lack of high-quality studies comparing these two techniques in order to certain the benefits and harms to use one of these 2 methods.

Objective

The purpose of the current study is to determine the effectiveness and safety of the LPS versus the VPS in patients with communicating hydrocephalus.

Methods and analysis

Patient and public involvement

No patient or public is involved in study design, recruitment or conduct of the study.

Study design and settings

The current study is a multi-center, open-label, and randomized controlled trial in which 550 patients with communicating hydrocephalus will be randomly allocated into LPS or LPS group in a ratio of 1:1. Patients will be enrolled at 20 neurosurgical centers in China Mainland that are experienced and skilled in both neurosurgery and shunt surgery. Each participating site will receive the local ethics committee approval, or obey our ethics committee review decision. We will propose the standardized procedures for CSF diversion and perioperative management before enrollment, and every attending neurosurgeon will be trained centrally. All patients will be fully informed the potential benefits, potential risks, and responsibilities, those who will sign the informed consents once they are included. This study protocol is developed following the Guidelines of Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).[20] The planned start date is Sep 2021 and end date is Jun 2028.

Sample size

A recent meta-analysis indicated the rate of VPS failure and LPS failure were 18.0% and 14.0%, respectively.[21] In this light, a sample of 250 for each group will be required in this trial while the significance level (two-sided) is 5% and the test power is 80%. Considering about the loss to follow-up within 2 years, the sample size is enlarged to

275 for each group.

Recruitment and eligibility criteria

Figure 1 shows the flow-chart of the selection of patients. The enrollment is expected to commenced in Sep 2021 and end in Dec 2025. Participants are recruited on outpatient department. Each participant will receive financial compensation. Specifically, once the eligible participants are admitted, 3-dimension brain and spine magnetic resonance imaging (MRI) scan will be performed to further evaluate the ventricles, aqueduct, basal cisterns, and spinal subarachnoid space, as well as to calculate the Evans index. Additionally, lumbar drainage is required to determine the eligibility.

Inclusion criteria

1. Age 18-90 years;
2. Symptomatic;
3. Communicating hydrocephalus;
4. Evans index > 0.3;
5. The communication of the ventricles with lumbar subarachnoid space is evident through lumbar puncture and CSF opening pressure is 70-200 mmH_2O

Exclusion criteria

1. Obstructive hydrocephalus;
2. Negative-pressure hydrocephalus;
3. Chiari malformation;
4. Prior history of shunt;
5. Lumbar fracture;
6. Decline to lumbar puncture.

Randomization and blinding

Subjects who meet the inclusion criteria and sign the informed consents will be randomly allocated into one of two groups in a ratio of 1:1. The randomized allocation using a random number table will be conducted by a designated member who will not involve in other activities of study patients. The randomization is not likely to blind for the subjects or attending neurosurgeons, but the data collectors, investigators, and

analysts are blinded.

Intervention

Neurosurgeons with extensive experience in the different procedures of CSF diversions will perform VPS or LPS, and will be trained centrally in advance and reach uniform standard. We will use the shunt system with programmable pressure valve, obtained from Medtronic (Minnesota, USA, LPS: 44421; VPS: 42866).

No matter which types of shunt system utilized, the initial pressure for the shunt system will set to the highest level before surgery.[22] If patients had no improvement in clinical symptoms after surgery, we will check the shunt function and lower the pressure setting by 1 step, monitoring the safety of patients.[23]

VPS

The patients in the supine position receive general anesthesia and then the head are turned to the left. A ventricular catheter is inserted into the lateral ventricle. A subcutaneous tunneler is made to connect the ventricles with abdominal cavity. The peritoneal catheter will be inserted if the CSF flow through shunt catheter is observed. The valve is placed at the cranial incision with a 3-point fixation to the subcutaneous tissue.

LPS

The patients in the left lateral position receive general anesthesia and then the head are turned to the left. A lumbar catheter is inserted through the L3/4 or 2/3 interlaminar space into the spinal subarachnoid space. A subcutaneous flank region is then made to fix the valve. A subcutaneous tunneler is made to connect the spinal subarachnoid space, frank region, and abdominal cavity. The peritoneal catheter will be inserted if the CSF flow through shunt catheter is observed.

Outcomes

Based on the study schedule (Table 1), all patients will be analyzed before shunt insertion, at the time of discharge, 1 month, 6 months, 12 months and 24 months postoperatively.

Primary outcome

The primary outcome measure is the rate of shunt failure at 2-year follow-up term. On the basis of previous studies, shunt failure is defined as the occurrence of shunt revision owing to shunt obstruction, breakage, tubing exposure, malfunction, disconnection, infection, or other conditions that require shunt revision. Shunt failure is also considered if improvement of symptoms or neurological function is not observed, corresponding to no improvement on the score of KHS, NIHSS, or GOS-E within 2 years at evaluation point. Shunt success is defined as the lack of shunt failure.

Secondary outcome

The secondary outcomes include Kiefer's Hydrocephalus Scale (KHS), National Institute of Health stroke scale (NIHSS), Glasgow Outcome Scale Extended (GOS-E), Evans index, and safety endpoints, within 2 years after shunt implantation, as well as the cost-effectiveness of hospital stay. As shown in Supplementary files, KHS, a scale proposed by Kiefer[24], consists of five items: gait disturbances, mental disorder, urinary incontinence, headache, and vertigo. The score of KHS ranges from 0 to 25 (higher is worse). The improvement of neurological function is evaluated by NHISS. A positive response to shunt implantation will be defined as an improvement of more than 1 point in the KHS or NIHSS at evaluation point. The axial brain magnetic resonance imaging (MRI) scan is used to calculate the Evans index, which is the ratio of frontal horn to biparietal diameter.

Safety endpoint include surgical complications, any adverse events, and length of stay. The common complications after shunt surgery include over-drainage, intracranial hemorrhage, infection, malfunction, shunt obstruction, shunt migration, shunt disconnection, new epilepsy, and abdominal symptoms. Severe adverse events (SAEs) refer to death, life-threatening events, shunt-related disability, hospitalization for emergencies or intensive care unit, or a prolonged hospitalization period.

The cost-effectiveness of hospital stay will synchronously be investigated since the implanted system is not similar and the postoperative cost will be associated to the occurrence and management of complications.

Data collection and management

All patients will be analyzed before shunt insertion, on the day of discharge, 1 month, 6 months, 12 months and 24 months postoperatively. At each site, 2 independent investigators will collect the baseline data such as age, gender, etiology, date of admission, comorbidities, Glasgow Coma Scale (GCS), symptoms, KHS, NIHSS, Evans index, CSF parameters, and CSF opening pressure. All patients will be follow-up on a regular basis by outpatient visits. All data from hospitalization and follow-up visits will be recorded in a paper-based table and then fixed into an electronic database. All data will be carefully examined and verified by these 2 investigators.

Statistical analysis

All data will be analyzed using the statistical software program SPSS version 19 (IBM, Armonk, New York). Probability values (*P*) less than 0.05 (2-side) is considered to have statistical difference. For pairwise comparison, Bonferroni Correction will be used, and the desired alpha-level (0.05) divided by the number of comparisons equals the *P*-value required for significance. Categorical variables are statistically descried as number (percent). We will use Chi-square test to compare the difference on categorical variables (Fisher's exact test is used while appropriate). As referring to quantitative data, we will use Kolmogorov-Smirnov test is to determine the normality. If quantitative data follows normal-distribution, described as arithmetic mean ± standard deviation (SD), we will use *t*-test to compare the difference. Other quantitative data will be described as median (range) and we will use Wilcoxon rank sum test to compare the difference. Shunt-success rate curve is obtained using the method of Kaplan-Meier and log-rank test is used to compare the difference between the 2 groups. The outcomes are presented as the incidence rate, or values, and its 95% confidence intervals, which will be calculated through SPSS program. We will use the Pearson's correlation to analyze the correlation between parameters.

Data and safety monitoring

We will set up a data monitoring committee (DMC) to guarantee the safety of this trial. All SAEs will be recorded in detail and reported to ethics committee. Members of the DMC will review all adverse events regularly, and hold a seminar to assess the risk and

safety of the study if necessary.

Data available statement

The datasets generated and analyzed during the current study are available from Research Manager (http://www.medresman.org.cn.), as well as the corresponding author on reasonable request.

Discussion

This study is currently the first randomized controlled trial comparing the two most commonly used techniques of shunt surgery (LPS and VPS) in the treatment of communicating hydrocephalus in order to provide high-level evidence. We believe that this trial is necessary since the benefits and harms to utilize one of these 2 methods are poorly understood. The results of the current study will provide high-level evidence for shunt-dependent hydrocephalus guidelines including the indications and contraindications to perform shunt, the standard procedures, and the optimal option. This trial will also help to create an algorithm for the selection of suitable patients, pre-shunt and post-shunt management.

Despite the potential strengths, there are some aspects of issues that need to be discussed. First, in this study, we will include symptomatic patients and asymptomatic patients will be excluded. The clinical manifestations of communicating hydrocephalus are various, such as gait/balance disturbance, dementia, urinary incontinence, headache, vertigo, psychiatric syndrome, etc. Patients with new or deteriorated symptoms that is estimated to be closely associated with hydrocephalus will be included in this trial. Elderly patients those who have at least one impairment of Hakim's triad and ventriculomegaly and are lack of known cause will be diagnosed as probably INPH, and Tap test, or external lumbar drainage, will be performed to determine the improvement of symptoms using KHS before allocation (Supplementary Figure 1). The evaluation for INPH will help to differentiate with Alzheimer disease and Parkinson's disease.

Second, KHS is chosen to evaluate the improvement of symptoms in this trial. Currently, there are no commonly accepted scales with the respect to the evaluation of symptoms

for communicating hydrocephalus. However, there are a number of clinical scales widely used in patients with INPH such as INPH grading scale (INPHGS) and Mini-Mental State Examination (MMSE), which are focusing on the typical syndrome of INPH (gait/balance disturbance, dementia, urinary incontinence).[10] Patients with communicating hydrocephalus are possible to develop various symptoms and signs. In this regard, KHS is a more appropriate scale since the five items of KHS are common symptoms for communicating hydrocephalus.[13,24] Besides, the combination of KHS with NIHSS in this trial are probably superior to accurately evaluate the neurological symptoms and function.

Last, in terms of CSF opening pressure, we believe that pressures that are dramatically higher or lower than a range are likely not suitable for the upcoming LPS surgery. According to the Western guideline for the diagnosis of INPH,[25] CSF opening pressure in the range of 70-245 mm H_2O is consistent with a probable NPH diagnosis but the range is suggested to be <200 mm H_2O based on the Japanese guidelines for the diagnosis of INPH.[26] In addition, there is no consensus in the optimal CSF opening pressure to perform LPS implantation. Taken together, a range of 70–200 mm H_2O is chosen in this study.

Ethics and dissemination

The study will be performed in compliance with the Declaration of Helsinki (2002) of the World Medical Association. The study was approved by Institutional Review Board of West China Hospital and registered through Chinese Clinical Trial Registry (ChiCTR) in March 2021. All patients will be fully informed the potential benefits, potential risks, and responsibilities, those who will sign the informed consents once they are included. Preliminary and final results will be published in peer-reviewed journals and presented at national and international congresses.

Authors' contributions

TS contributed to conceptualization, methodology, quality assessment, and writing original draft. WC and JY contributed to data curation, software, and formal analysis. YY and YZ contributed to investigation. XL and HY contributed to formal analysis and

writing original draft. CY contributed to conceptualization, quality assessment, and manuscript revision. JG contributed to conceptualization, quality assessment, supervision, funding acquisition, and manuscript revision. All authors approved the final manuscript.

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Competing interests

None declared.

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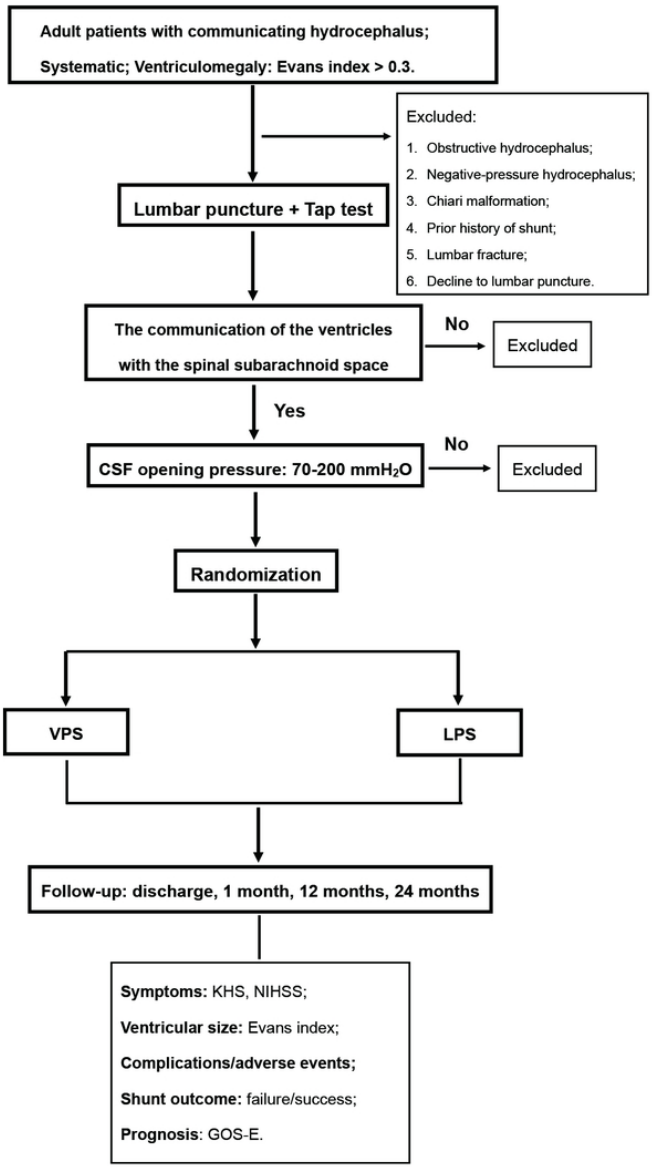
Figure 1 Flow chart of the selection pf patients. VPS, ventriculoperitoneal shunt; LPS, lumboperitoneal shunt; CSF, cerebrospinal fluid; Keifer's Hydrocephalus Scale; NIHSS, National Institute of Health stroke scale; GOS-E, Glasgow Outcome Scale

Extended.

Table 1 Study schedule

	Baseline	Discharge	1 month	12 months	24 months
KHS	√	√	√	√	√
NIHSS	√	√	√	√	√
GOS-E	√	√	√	√	√
Evans index	√	√	√	√	√
Shunt outcome†		√	√	√	√
Complications		√	√	√	√
Mortality		√	√	√	√
Cost-effectiveness		√			

Evans index will be calculated through the magnetic resonance imaging (MRI) scan.
† "Shunt outcome" includes shunt failure and shunt success.
KHS, Keifer's Hydrocephalus Scale; NIHSS, National Institute of Health stroke scale; GOS-E, Glasgow Outcome Scale Extended.



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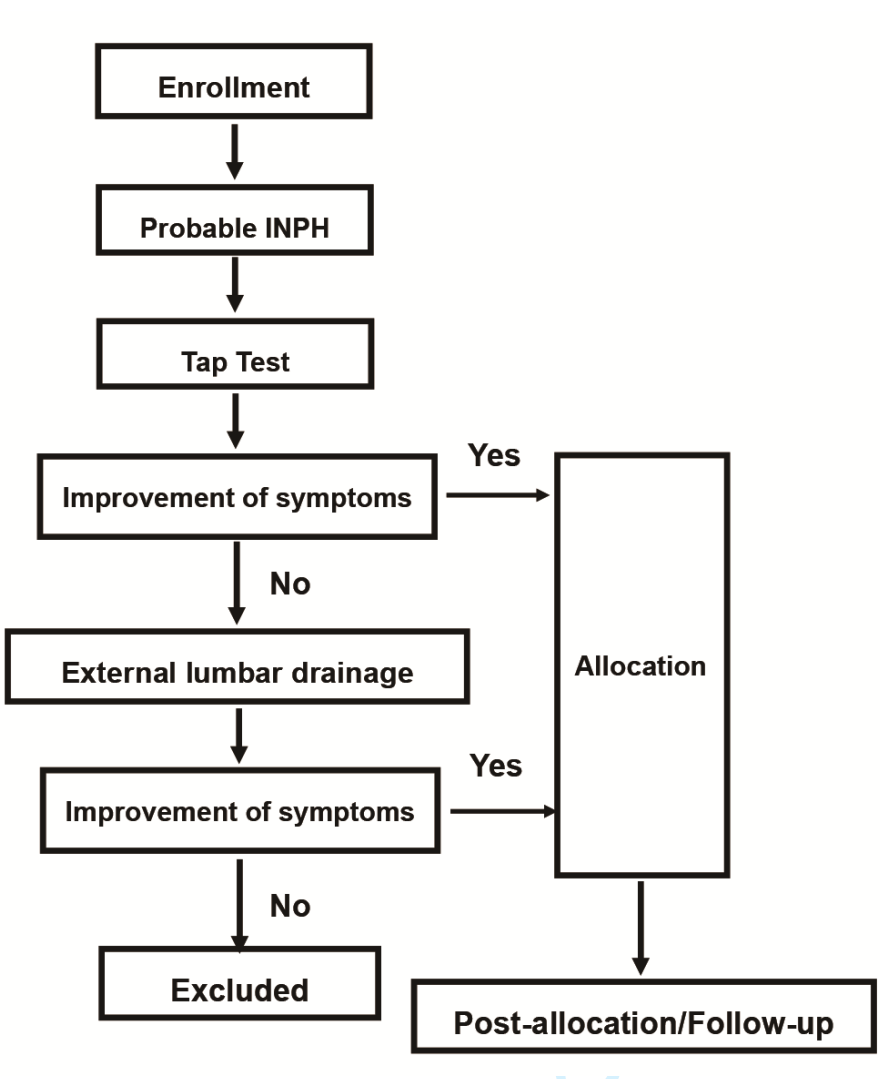
Supplementary Figure 1. The selection of patients with probable idiopathic normal-pressure hydrocephalus. INPH, idiopathic normal-pressure hydrocephalus



Keifer's Hydrocephalus Scale

Item	Clinical features	Score
Mental state	No clinical detection	**0**
	Concentration disorders, forgetfulness	**1**
	Apathy, orientated only in parts and symptoms of Score 1	**3**
	Completely disorientated, skill disorders	**5**
Gait disorders	No gait disorders, or gait disorders only detectable in special tests (i.e., walking with closed eyes)	**0**
	Gait is ataxic and wide-based, but secure (without help)	**2**
	Walking is difficult and only possible with help	**4**
	Only a few steps with help of others	**5**
	Impossible to walk	**6**
Incontinence	No incontinence	**0**
	Temporary incontinence (e.g., at night)	**3**
	Permanent incontinence	**4**
	Incontinence of urine and stool	**6**
Headache	No headache	**0**
	Intermittent (e.g., at night) or permanent, slight-headache	**1**
	Heavy, permanent headache	**4**
Vertigo	no vertigo	**0**
	vertigo only under stress	**1**
	intermittent vertigo	**3**
	Permanent vertigo	**4**
Total		

National Institute of Health stroke scale (NIHSS)

Item	Clinical features	Score
Level of consciousness	Alert	**0**
	Not alert, arousable	**1**
	Not alert, obtunded	**2**
	Unresponsive	**3**
LOC questions	Answers both correctly	**0**
	Answers one correctly	**1**
	Incorrect	**2**
LOC commands	Obeys both correctly	**0**
	Obeys one correctly	**1**
	Incorrect	**2**
Gaze	Normal	**0**
	Partial gaze palsy	**1**

	Forced deviation	**2**
Visual fields	No visual loss	**0**
	Partial hemianopsia	**1**
	Complete hemianopsia	**2**
	Bilateral hemianopsia	**3**
Facial palsy	Normal	**0**
	Minor paralysis	**1**
	Partial paralysis	**2**
	Complete paralysis	**3**
Motor arm (a) Left (b) Right	No drift	**0**
	Drift before 10 s	**1**
	Falls before 10 s	**2**
	No effort against gravity	**3**
	No movement	**4**
Motor leg (b) Left (b) Right	No drift	**0**
	Drift before 10 s	**1**
	Falls before 10 s	**2**
	No effort against gravity	**3**
	No movement	**4**
Ataxia	Absent	**0**
	One limb	**1**
	Two limbs	**2**
Sensory	Normal	**0**
	Mild loss	**1**
	Severe loss	**2**
Language	Normal	**0**
	Mild aphasia	**1**
	Severe aphasia	**2**
	Mute or global aphasia	**3**
Dysarthria	Normal	**0**
	Mild	**1**
	Severe	**2**
Extinction/inattention	Normal	**0**
	Mild	**1**
	Severe	**2**
Total		

LOC, level of consciousness

Glasgow Outcome Scale Extended (GOS-E)

Item	Score
Dead	1
Vegetative state	2
Lower severe disability	3
Upper severe disability	4
Lower moderate disability	5
Upper moderate disability	6
Lower good recovery	7
Upper good recovery	8

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 2
	2b	All items from the World Health Organization Trial Registration Data Set	Page 2
Protocol version	3	Date and version identifier	-
Funding	4	Sources and types of financial, material, and other support	Page 11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 1 and 11
	5b	Name and contact information for the trial sponsor	-
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	-
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Page 5 and 9
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 4
	6b	Explanation for choice of comparators	Page 4
Objectives	7	Specific objectives or hypotheses	Page 5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 5 and 6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 6 and 7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page 6 and 7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 6 and 7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 6 and 7

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 7 and 8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 7, Table 1, and Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 5
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 6
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 8 and 9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 9
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 9
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page 9
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 9

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 9
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Page 11
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 8 and 11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 11
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 11
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary files
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.