Preoperative evaluation using external lumbar drainage for patients with posthemorrhagic hydrocephalus
A prospective, monocentric, randomized controlled trial
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Abstract
Background: External lumbar drainage (ELD) remains the most common used methods with a higher sensitivity before lumboperitoneal shunt (LPS) implantation to predict the shunt outcomes in the treatment of idiopathic normal pressure hydrocephalus. However, the benefits of such supplemental test have not been tested in the treatment of post-hemorrhagic hydrocephalus (PHH).

Methods and design: In the current trial, 100 eligible patients with PHH will be recruited and randomly assigned to the ELD group (study group) and non-ELD group (control group). Lumbar puncture (LP) will be performed for participants in non-ELD group. LP plus ELD will be performed for participants in ELD group, those who will then be investigated the suitability of potential LPS 4 days after ELD. Two independent and practiced assessors will collect the baseline data and evaluate each participant 4 days after ELD or LP, 1 day after LPS, at the time of discharge and 1 month after LPS. The primary outcome is the shunting outcomes 1 month after surgery. The secondary outcomes include the complications related to ELD, complications related to LPS, and Evens index at each evaluation point. Meanwhile, serious adverse events occurring at any time is recorded to determine the safety of this trial.

Discussion: The results of this trial will demonstrate whether preoperative evaluation using temporary ELD for patients with PHH could attenuate the risk of LPS failure.

Trial registration number ChiCTR2000034094; Pre-results.

Abbreviations: ELD = external lumbar drainage, LP = lumbar puncture, LPS = lumboperitoneal shunt, PHH = post-hemorrhagic hydrocephalus.

Keywords: clinical outcomes, comparison, external lumbar drainage, lumboperitoneal shunt, post-hemorrhagic hydrocephalus, randomized controlled trial

1. Introduction
Since the application of shunt surgery in clinic, a great deal of attention was directly given to quest the path to attenuate the incidence of shunt failure.[1,2] To date, preoperative accurate evaluation through supplemental test has been widely accepted to correctly select the suitable patients for shunt implantation.[3,4] In this regard, external lumbar drainage (ELD) remains the most common used methods with a higher sensitivity before lumboper-
ileal shunt (LPS) implantation to predict the shunt outcomes in the
treatment of idiopathic normal pressure hydrocephalus. However,
the benefits of such supplemental test have not been tested in the
treatment of post-hemorrhagic hydrocephalus (PHH), a common
disease occurring secondary to intracranial hemorrhage.

2. Methods and design

2.1. Objective

To prove whether preoperative evaluation using ELD for patients
with PHH could attenuate the risk of LPS failure.

2.2. Study design

The flow chart of the selection of patients is shown in Figure 1. In
the current trial, 100 eligible patients with PHH will be recruited
from the Department of outpatient of Sichuan University West
China Hospital since September 1, 2020, and randomly assigned
to the ELD group (study group) and non-ELD group (control
group). Lumbar puncture (LP) will be performed for participants
in non-ELD group. LP plus ELD will be performed for participants in ELD group, those who will then be investigated
the suitability of potential LPS 4 days after ELD. Two
independent and practiced assessors will collect the baseline
data and evaluate each participant 4 days after ELD or LP, 1 day
after LPS, at the time of discharge and 1 month after LPS. The
primary outcome is the shunting outcomes 1 month after surgery.
The secondary outcomes include the complications related to
ELD, complications related to LPS, and Evens index at each
evaluation point. Meanwhile, serious adverse events occurring at
any time is recorded to determine the safety of this trial.

2.3. Recruitment and eligibility

2.3.1. Inclusion criteria.

1. Age >18 years;
2. Ventricular expansion occurring secondary to intracranial
hemorrhage;
3. Evans index >0.3;
4. LP indicates that the subarachnoid space of spinal cord is
connected with ventricles, and the cerebrospinal fluid opening
pressure is between 70 and 200 mm Hg.

2.3.2. Exclusion criteria.

1. Obstructive hydrocephalus;
2. Decline to ELD or LPS surgery;
3. Skull defect.

2.4. Sample size

Previously published reports indicated that the rate of LPS failure for
patients with preoperative evaluation using ELD was 15.7%,
comparing with a rate of 40.9% for patients without ELD. In
this regard, a sample of 45 will be required in this trial with a significance
level of 5% (2-sided) and a power of 80% to demonstrate a 20% difference in rate of shunt failure. Considering about the loss to
follow-up, the sample size is enlarged to 50 for each group.

2.5. Randomizing and blinding

The randomization will be performed using a random number
table that is generated by the statistical program SAS Version 9.4
(SAS Institute Inc, Cary, NC) and is kept secret by the statisticians
who are independent of this study. This trial is open-label, but
assessors and analysts are blind to allocation and the intervention
clinicians will not involve in any assessment.

2.6. Intervention

Physicians, neurosurgeons, and clinicians will be trained centrally
in advance and reach uniform standard.
2.7. Temporary ELD

ELD is performed under local infiltration anesthesia and the patients are positioned in the left lateral position. A lumbar catheter is inserted through the L3/4 or L2/3 interlaminar space into the spinal subarachnoid space and then connected to the drainage system. According to previous studies, the drainage period is 3 days and drainage volume is 150 to 200 mL per 24 hours.[8]

2.8. Preoperative evaluation

Repeated evaluation will be performed using the scale, as shown in Table 1, 4 days after ELD to investigate the suitability of potential LPS and then the ELD system will be removed. Patients with scores 4 will be included in this trial and the remaining patients will be excluded. Specifically, the improvement of clinical manifestation is defined as an improvement of 1 point or more in the National Institute of Health stroke scale, Glasgow coma scale, modified Rankin scale, or according to self-assessment.

2.9. Outcomes

Two independent and practiced assessors will collect the baseline characteristics and evaluate each participant 4 days after ELD or LP, 1 day after LPS, at the time of discharge and 1 month after LPS. The evaluation schedule is shown in Table 2.

2.9.1. Primary outcome. The primary outcome is the shunting outcomes 1 month after surgery. Shunting outcomes include shunt failure and shunt success. According to previous studies, which is defined as the shunt obstruction, breakage, tubing exposure, malfunction, or infection requiring shunt revision. Shunt success is defined as the absence of shunt failure.

2.9.2. Secondary outcomes. The secondary outcomes include the complications related to ELD, complications related to LPS, and Evens index at each evaluation point.

Meanwhile, considering about the safety of this trial, serious adverse events occurring at any time is recorded.

2.10. Data collection

Two independent and practiced assessors will collect the data. All data will be recorded in the paper-based Case Record Form and Electronic Data Capture. A third reviewer is required while there are any debates on data collection.

2.11. Data and safety monitoring

Members of independent data monitoring committee, including 1 physician, 1 statistician, and 1 data analyst, are responsible for monitoring the safety and efficacy of this trial once a month.

2.12. Statistics analysis

SPSS version 19 (IBM, Armonk, NY) is used to analyze statistics and a P-value (2-sided) under .05 is considered to have statistical difference. Kolmogorov–Smirnov test is first used to determine the normality of quantitative data. Quantitative data followed normal-distribution are statistically described as arithmetic mean ± standard deviation. Other quantitative data (non-normal distribution) are statistically described as median (range). Categorical data, such as sex, shunting outcomes, and complications, are statistically described as number (percent). To compare the 2 groups on quantitative data followed normal-distribution, the independent samples t-test is used. To compare the 2 groups on the other quantitative data, Wilcoxon rank sum test is used. To compare the 2 groups on categorical data followed normal-distribution, Chi-square test is used.

2.13. Withdrawal and dropout

If at least 2 researchers judge that it is not appropriate to continuously participant in this trial, or any participants choose to withdraw, they are kindly suggested to stop the ongoing intervention and receive appropriate medical treatment.

### Table 1

| Scores | Clinical manifestation | Protein in CSF | Nucleated cells in CSF | Red blood cells in CSF |
|--------|------------------------|---------------|------------------------|------------------------|
| 1      | Improvement            | <=0.45 g/L    | <=10^6 /L              | <=100 × 10^6 /L        |
| 0      | Invariant or aggravated| >0.45         | >10^6 /L               | >100 × 10^6 /L         |

2SF = cerebrospinal fluid, ELD = external lumbar drainage.

### Table 2

|                      | Baseline | 4 d after ELD or LP† | 1 d after LPS | Discharge | 1 mo after LPS |
|----------------------|----------|----------------------|---------------|-----------|---------------|
| NIHSS                | ✓         | ✓                    | ✓             | ✓         |               |
| GCS                  | ✓         | ✓                    | ✓             | ✓         |               |
| mRS                  | ✓         | ✓                    | ✓             | ✓         |               |
| Head imaging         | ✓         | ✓                    | ✓             | ✓         |               |
| Shunt outcome*       | ✓         | ✓                    | ✓             | ✓         |               |
| Complications related to ELD | ✓       | ✓                    | ✓             | ✓         |               |
| Complications related to LPS | ✓       | ✓                    | ✓             | ✓         |               |
| SAEs                 | ✓         | ✓                    | ✓             | ✓         |               |

ELD = external lumbar drainage, GCS = Glasgow coma scale, LP = lumbar puncture, LPS = lumboperitoneal shunt, mRS = modified Rankin scale, NIHSS = National Institute of Health stroke scale, SAEs = serious adverse events.

* Shunt outcome* includes shunt failure and shunt success.
† ELD will be performed for patients in study group (ELD group) and LP will be performed for patients in control group (non-ELD group).
withdrawal and dropout, the reasons of withdrawal and dropout will be recorded and submitted to the supervisor for review.

3. Discussion
This study will be the first randomized controlled trial that analyzes the clinical outcomes of patients diagnosed as PHH with or without evaluation using temporary ELD before LPS implantation. The results of this trial will demonstrate whether preoperative evaluation using temporary ELD for patients with PHH could attenuate the risk of LPS failure and generate the discussion about the accurate evaluation of the suitability of shunt surgery through supplemental test. Additionally, the trial will provide the evidence for the association of shunt failure with the cerebrospinal fluid count and protein level.

The current trial, however, still has some limitations. First, it is a single-center study. Second, medical conditions and surgeons’ experiences are contributed to the postoperative outcomes. In this regard, personnel will be trained centrally in advance and reach uniform standard.

Author contributions
Conceptualization: Junwen Guan, Chao You, Tong Sun.
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Study design: Tong Sun, Junwen Guan.

Supervision: Chao You.
Validation: Chao You.
Writing – original draft: Tong Sun.
Writing – review & editing: Junwen Guan, Chao You, Yicheng Zhou.

References
[1] Marmarou A, Bergsneider M, Klinge P, et al. The value of supplemental prognostic tests for the preoperative assessment of idiopathic normal-pressure hydrocephalus. Neurosurgery 2005;57(3 Suppl):S17–28.
[2] Walchenbach R. The value of temporary external lumbar CSF drainage in predicting the outcome of shunting on normal pressure hydrocephalus. J Neurol Neurosurg Psychiatry 2002;72:503–6.
[3] Mahr CV, Dengl M, Nestler U, et al. Idiopathic normal pressure hydrocephalus: diagnostic and predictive value of clinical testing, lumbar drainage, and CSF dynamics. J Neurosurg 2016;125:591–7.
[4] Yamada S, Ishikawa M, Miyajima M, et al. Disease duration: the key to accurate CSF tap test in iNPH. Acta Neurol Scand 2017;135:189–96.
[5] Raneri F, Zella MAS, Di Cristofori A, et al. Supplementary tests in idiopathic normal pressure hydrocephalus: a single-center experience with a combined lumbar infusion test and tap test. World Neurosurg 2017;100:567–74.
[6] Karimy JK, Zhang J, Kurland DB, et al. Inflammation-dependent cerebrospinal fluid hypersecretion by the choroid plexus epithelium in posthemorrhagic hydrocephalus. Nat Med 2017;23:997–1003.
[7] Sun T, Yuan Y, Zhang Q, et al. Establishing a preoperative evaluation system for lumboperitoneal shunt: approach to attenuate the risk of shunt failure. World Neurosurg 2018;117:e308–15.
[8] Lenfeldt N, Hansson W, Larsson A, et al. Three-day CSF drainage barely reduces ventricular size in normal pressure hydrocephalus. Neurology 2012;79:237–42.