PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Shunting outcomes in communicating hydrocephalus: Protocol for
	a multi-center, open-label, randomized controlled trial
AUTHORS	Sun, Tong; Cui, Wenyao; Yang, Jingguo; Yuan, Yikai; Li, Xuepei;
	Yu, Hang; Zhou, Yicheng; You, Chao; Guan, Junwen

VERSION 1 – REVIEW

REVIEWER	Gholampour, Seifollah Islamic Azad University Tehran North Branch
REVIEW RETURNED	14-May-2021

	Deer Editor
GENERAL COMMENTS	Deal cultur There you for inviting me on a reviewer of this paper.
	I hank you for inviting me as a reviewer of this paper.
	This topic is interesting and the findings can be useful for
	neurosurgeons. The results are valuable but the authors have
	written some big claims in the main manuscript that they have to
	rewrite those sentences. I couldn't find the detailed results about
	the calculation and measurement of KHS, NIHSS, GOS-E, Evans
	index, and safety endpoints. These details are really necessary to
	insurance about the correctness of findings. The statistical analysis
	is incomplete. Effects of some variables such as brands or
	functions of Shunts, and being INPH or non-INPH of patients are
	unclear in the manuscript. I couldn't find the letters and evidence
	about Consents, Ethics, and Clinical trials. They are really
	necessary for this article. Of course, maybe the editorial manager
	did not send me these documents. Furthermore, I am not an
	expert to make a decision about the quality of the English
	Language Level of the text of this manuscript.
	Taken together I believe this manuscript after considering the
	following comments can be published in the BMJ Open
	MAJOR COMMENTS:
	1- "about comparing the two most popular surgical methods in
	the treatment " I umboperitoneal shunt is not a common method
	So don't use the word "most popular"
	2- "The current study will provide to provide methods"
	"whether LPS is the ontimal option in patients with communicating
	hydrocenhalus is unclear"
	Rewrite the aforementioned sentences
	3- "This study will provide the evidence on the indications and
	contraindications to perform Shunt the standard procedures and
	the optimal option "
	There are numerous studies in previous researches that showed
	these contraindications about performing Shunts and/or their
	antimal option. Where are the Strengths or limitations of this itom?
	4 "Medical condition and experience of ettending currence are
	4- medical condition and experience of altending surgeons are
	Various.
	Is this a Strength of your study!

	 5- "LPS has some advantages over VPS, including the avoidance of brain injury and lower incidence of infection.14" Could you clarify which section (sentence number and page number) of Ref 14 that indicated the above sentence? 6- "Currently, there are no randomized studies comparing the efficacy of these 2 techniques." I couldn't approve or disapprove this claim. But it would be better if you don't use these sentences in a scientific paper. There are many valuable works, and we are optimistic that your results can improve the previous findings. 7- For a comprehensive assessment of the efficiency of VPS, and also mentioning and comparing with other treatment methods such as ETV that you don't mention in the Introduction, you can use these Refs: 10.1016/j.cmpb.2021.106049 and 10.1371/journal.pone.0196216. 8- We know there are various reasons for occurring CH. But the most valuable findings of your work could be related to elderly CH and INPH, since, their causes are known. Accordingly, it would be better if you can separate your results based on the corresponding results of these patients specifically. So, despite your results are valuable for all patients, but now only this part of your findings could be necessary for neurosurgeons since generally neurosurgeons can handle other patients. 9- "Considering about the loss to follow-up" Clarify this sentence. Do you follow-up the patients for 2 years or not. 10- Your title is about Communicating Hydrocephalus. Are you sure about using the words obstructive hydrocephalus, Nonobstructive are similar to non-communicating nydrocephalus in the manuscript?. Do you think the definitions of obstructive or nonobstructive are similar to non-communicating nydrocephalus in the manuscript?
	obstructive are similar to non-communicating or communicating? Reassess these words in the manuscript. 11- "Medtronic (USA) Sophysa". Clarify the particular type of Shunts with the codes and numbers. You have used shunts with two brands (Medtronic and Sophysa). Were there any differences between the results of these two brands on your patients? Did this variable effective on your results?
	 12- I couldn't find any detailed results about the calculation and measurement of KHS, NIHSS, GOS-E, Evans index, and safety endpoints! Add all of these details like Tables, Charts, Figures, Diagrams and some images from your patients. 13- Probability values (P) are considered 0.05. Do you assess Bonferroni Correction in your statistical analysis? Is there dependency between the parameters? Particularly about the parameters with geometrical dimensions. Furthermore, add the results of the confidence interval assessment. 14- Comparisons of your results with the results of previous papers
	are poor. For example, according to the findings of Giordan et al., the failure rate of VPS and LPS were 18.0% and 14.0%, respectively. Can you compare this result with your findings? What about other papers or other parameters? Because despite the novelty of your work, some parts of your results are comparable with previous works.
REVIEWER	Guevara Carlos

REVIEWER	Guevara, Carlos Hospital Clínico de la Universidad de Chile José Joaquín Aguirre
REVIEW RETURNED	23-May-2021

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	This produces have been as a first him off and the second se
GENERAL COMMENTS	i his protocol represents a big effort to progress in the surgical
	outcome in such
	poorly studied disease such as communicating hydrocephalus.
	However, I have concerns on the inclusión criteria which do not
	well characterize to those patients to be included, in particular, it
	looks like asymptomatic patients with an Evans index > 0, 3 can be
	Included in these surgical procedures
	It is not described which are the symptoms and signs of a
	symptomatic patients with communicating hydrocephalus, whether
	in a symptomatic patient the Hakim's triad will be considered, or
	whether parkisnonism will be explored.
	In the primary outcomes, shunt failure included not improvement of
	symptoms or neurological functions. So I think that the magnitude
	of deterioration/improvement of these manifestations should be
	clear.
	In other hand, related to the inclusión criteria, there are studies
	that suggest that an Evan Index >0,3 may be found in 30% percent
	of healthy elderly controls (Brix 2017, Eur J Radiol). The author
	may consider to explain why they will not use the tap test in the
	diagnostic workup.
	In summary, for this reviewer is not clear how asymptomatic
	patients will be excluded of this trials, and how other diseases
	such as parkinsonism and hydrocephalus will be studied previous
	to the procedures and finally which are the magnitude of the
	changes in the clinical scales for deterioration/ improvement after
	the surgical procedures

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:

- 1. We are so sorry for using the word "most popular". It has been changed as "these 2 procedures of CSF diversions".
- 2. We are so sorry for the mistakes. "to provide" has been deleted and "whether LPS is the optimal option in patients with communicating hydrocephalus is unclear" has been changed as "the comparison of VPS to LPS in the treatment of communicating hydrocephalus is poorly understood."
- 3. This item of Strengths or limitations has been addressed, and now, it is "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. We are so sorry for the unclear description. Considering about the evaluation of 2 surgical methods in this trial, the limitation is the various skills and practice but the neurosurgeons will be trained centrally in advance and reach uniform standard.
- 5. Ref 14 (Wang VY, Barbaro NM, Lawton MT, et al. Complications of lumboperitoneal shunts. Neurosurgery. Jun 2007;60(6):1045-1048; discussion 1049.), in the revised manuscript it is Ref 17. In the section of introduction, the second paragraph "First and foremost, using LP shunts allows the surgeon to avoid the need to access ventricular cavities within the brain parenchyma, and thereby potentially reduces the risk of brain injury (such as cortical venous injury or hemorrhage) from catheter placement. LP shunts are also reported to be associated with a lower infection rate than

VP shunt". We are sorry for the misunderstanding. The words "avoidance" is not appropriate. In the revised one, it has been changed as "LPS has some advantages over VPS, including the lower risk of brain injury and lower incidence of infection."

- 6. Indeed, "there are no randomized studies" is not appropriate in a scientific paper. We have changed it as "there are few prospective studies".
- 7. Thank you for your valuable and constructive recommendation. We have carefully read these 2 papers, which have been added to the section of Reference. Meanwhile, we have discussed ETV in Introduction. "Endoscopic third ventriculostomy (ETV) is an alternative and effective option for obstructive hydrocephalus, and has recently been performed for communicating types of hydrocephalus. 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."
- Thank you for your valuable and constructive suggestions. The subgroup analysis regarding different etiologies (ICH, TBI, idiopathic, etc), different results of preoperative evaluation (Tap test), and CSF parameters have been planned previously.
- 9. We are so sorry for the unclear description. Each patient will follow-up for 2 years. It is inevitable that a few patients will be loss to follow-up so we enlarged the sample size.
- 10. We are so sorry for the unclear description. We will use the words "communicating hydrocephalus" and "obstructive hydrocephalus".
- 11. After careful consideration and discussion, we will only use the shunt system with programmable pressure value obtained from Medtronic. The codes and numbers have been attached in the revised manuscript.
- 12. The evaluation methods, details, interpretation of KHS, GOS-E, and INHSS have been provided in the supplementary files. The method to calculate Evans index has been added.
- 13. The potential complications regarding safety endpoints have been added. 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) include death, life-threatening events, shunt-related disability, hospitalization for emergencies or intensive care unit, or a prolonged hospitalization period.
- 14. 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. 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.
- 15. The calculation of sample size remains controversial. In this trial, the incidence rate of shunt failure is the main endpoint. There are numerous studies analyzing the failure of VPS but the failure rate of LPS is poorly understood. For instance, in 1990, Aoki et, al.¹ had ever reported the rate of LPS failure was 14%. In 2004, Karabatsou et, al. ² showed eighteen patients (85.7%) underwent shunt failure after LPS. In 2007, Wang et, al.³ showed 37 of 67 (55.2%) underwent shunt failure after LPS.

Miyajima et, al.⁴ showed 7% underwent shunt failure after LPS. But these LPS-related studies are retrospective, or analyze small size of patients. There are few studies providing high-quality evidence. Giordan et. al⁵ recently performed a systematic review and meta-analysis. Their study systematically analyzed relatively large number of patients with NPH treated by LPS or VPS, which is, to date, appropriate and accurate to be utilized to calculate the sample size. Besides, the number of patients (275) for each group is relatively large to date comparing other studies.

Reference

- 1. Nobuhiko A. Lumboperitoneal shunt: clinical applications, complications, and comparison with ventriculoperitoneal shunt. Neurosurgery. 1990(6):998-1003.
- 2. Karabatsou K, Quigley G, Buxton N, Foy P, Mallucci C. Lumboperitoneal shunts: are the complications acceptable? Acta neurochirurgica. Nov 2004;146(11):1193-1197.
- 3. Wang VY, Barbaro NM, Lawton MT, et al. Complications of lumboperitoneal shunts. Neurosurgery. Jun 2007;60(6):1045-1048; discussion 1049.
- 4. Miyajima M, Kazui H, Mori E, Ishikawa M, Sinphoni-Investigators obot. One-year outcome in patients with idiopathic normal-pressure hydrocephalus: comparison of lumboperitoneal shunt to ventriculoperitoneal shunt. Journal of neurosurgery. Dec 2016;125(6):1483-1492.
- 5. Enrico G, Giorgio P, Giuseppe L, Mohammad Hassan M, Benjamin DE. Outcomes and complications of different surgical treatments for idiopathic normal pressure hydrocephalus: a systematic review and meta-analysis. Journal of Neurosurgery JNS. 01 Oct. 2019 2019;131(4):1024-1036.

Reviewer #2:

- Thank you for your valuable and constructive suggestions. In general, in clinical practice, we will only preform shunt surgery for symptomatic patients while asymptomatic patients are likely to select conservative treatments and regular follow-up. We are so sorry for the unclear description about the inclusion criteria. The item "symptomatic" has been added in the section of inclusion criteria.
- 2. 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.
- 3. We are so sorry for the unclear description. The not improvement of symptoms or neurological functions is defined as no improvement on the score of KHS, NIHSS, or GOS-E within 2 years at evaluation point.
- 4. I cannot agree with you any more regarding "an Evan Index >0,3 may be found in some healthy elderly controls". In this light, 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. These contents have been discussed in the revised manuscript.

VERSION 2 – REVIEW

REVIEWER	Gholampour, Seifollah
	Islamic Azad University Tehran North Branch
REVIEW RETURNED	13-Jul-2021
GENERAL COMMENTS	The author have considered the comments.
REVIEWER	Guevara, Carlos
	Hospital Clínico de la Universidad de Chile José Joaquín Aguirre
REVIEW RETURNED	21-Jul-2021
GENERAL COMMENTS	Thank you for clarifying the inclusion criteria related to symptomatic patients