

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparative effectiveness of different surgical procedures for traumatic acute epidural hematoma: study protocol for Prospective, Observational Real-world Treatments of AEDH in Large-scale Surgical Cases (PORTALS-AEDH)
AUTHORS	Yang, Chun; Hui, Jiyuan; XIE, LI; Feng, Junfeng; Jiang, Jiyao

VERSION 1 – REVIEW

REVIEWER	Umana , GE Cannizzaro Hospital
REVIEW RETURNED	13-May-2021

GENERAL COMMENTS	<p>I thank the authors for this interesting study protocol, of great value for TBI patients. The topic is relevant and could influence the TBI guidelines, improving patient's care.</p> <p>I suggest to consider also rare delayed complications 10.1016/j.wneu.2019.12.179 and the cases of delayed hematoma development 10.1016/j.wneu.2019.10.009 and discuss their impact on the study.</p> <p>Congrats</p>
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REVIEWER	Wang, Xuanzhi University of Science and Technology of China
REVIEW RETURNED	03-Jun-2021

GENERAL COMMENTS	The authors plan to present a multicentre prospective, observational study of surgical strategies for AEDH, especially for the effectiveness of two major surgical treatments, hematoma
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	<p>evacuation craniotomy and hematoma evacuation with decompressive craniectomy. This study is necessary and meaningful. Here are some comments as follows:</p> <ol style="list-style-type: none"> 1. For Inclusion Criteria, why is subtentorial hematoma(EDH) excluded? 2. As mentioned by the authors, most acute epidural hematomas do not require decompressive craniectomy. Is the removal of bone flap related to pupil dilation time? Postoperative cerebral infarction may also be preoperative hypotension, preoperative thrombus shedding. 3. This research is time-consuming and involves a lot of staff. How to control the quality of the research. For example, neurosurgeons in different hospitals have different surgical skills and different opinions on whether bone flaps need to be removed during surgery. These all affect the results of the research . In addition, in China, for emergency surgical treatment of AEDH, neurosurgeons are junior doctors, how to ensure the quality of surgical treatment.
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REVIEWER	Laeke, Tsegazeab Addis Ababa University
REVIEW RETURNED	07-Jun-2021

GENERAL COMMENTS	<p>It is an elaborate manuscript.I have however some points to raise.One of the points is that for AEDH patients the primary treatment modality is craniotomy.DC is only done when the patient has infarction as a result of rain herniation not for AEDH. And intra cerebral hemorrhage and infarction are the exclusion criteria for the study.It will be better if you describe what the customary indication for DC is for AEDH and the details for the surgical techniques.</p> <p>- The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.</p>
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REVIEWER	Hayfron-Benjamin, Charles University of Ghana Medical School, Physiology
REVIEW RETURNED	26-Sep-2021

GENERAL COMMENTS	<p>COMMENTS</p> <p>Yang et al. present a multicenter, prospective, and observational real-world study protocol aimed at evaluating different surgical treatment options for acute epidural hematoma. This proposed study is important and has the potential to fill important gaps in the public literature on the surgical management of acute epidural hematoma. The comparative effectiveness research design is appropriate for comparing the two forms of active surgical treatment for acute epidural hematoma. However, I have some comments and recommendations.</p> <ol style="list-style-type: none"> 1. There are language/grammar errors in some portions of the manuscript. The authors should consider running the revised draft through a grammar checker. The tenses should also be
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	<p>appropriate/consistent; this is a protocol and the study is yet to be conducted.</p> <p>2. There are some discrepancies between the protocol published on ClinicalTrials.gov (NCT 04229966) and the current manuscript (protocol) draft. For example in the current draft, the age range in the eligibility criteria is 18 to 65 years. Under the recruitment information on ClinicalTrials.gov, the stated age range is ≥ 16 years. While revisions may be acceptable, they should be clarified/justified, especially as you refer to the trial registration in the protocol, and mentioned that the protocol has already been approved by the ethics committee/institutional review board of Renji Hospital.</p> <p>3. The authors should clarify how they will address bias in the comparative effectiveness study design</p> <p>4. The methods section may benefit from a sentence/paragraph indicating the current status of the study. Authors should also consider rephrasing "Patients recruitment will start in April 2021..." to reflect the fact that this was an anticipated start time.</p> <p>5. When a participant withdraws consent or decides to quit from the trial (especially those who had surrogates/legal representatives consenting on their behalf), will information previously collected be included in the analyses?</p> <p>6. Conspicuously missing in the discussion section is the limitations of this study, including the study design.</p> <p>7. Non-standard abbreviations should be defined on first use (e.g. ICP)</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. GE Umana, Cannizzaro Hospital

Comments to the Author:

I thank the authors for this interesting study protocol, of great value for TBI patients. The topic is relevant and could influence the TBI guidelines, improving patient's care.

I suggest to consider also rare delayed complications 10.1016/j.wneu.2019.12.179 and the cases of delayed hematoma development 10.1016/j.wneu.2019.10.009 and discuss their impact on the study.

Congrats

Reply:

- 1) We appreciate your encouraging comments.
- 2) We fully agree with the reviewer that delayed hematoma development is rare but significant to the management for EDH. We made adjustments accordingly in **Discussion** section. Please see **page 20** of the revised manuscript, **lines 8–11**.

Reviewer: 2

Dr. Xuanzhi Wang, University of Science and Technology of China

Comments to the Author:

The authors plan to present a multicentre prospective, observational study of surgical strategies for AEDH, especially for the effectiveness of two major surgical treatments, hematoma evacuation craniotomy and hematoma evacuation with decompressive craniectomy. This study is necessary and meaningful. Here are some comments as follows:

Reply:

Thank you for your positive comment on this study. We appreciate your encouragement and the specific suggestions for improving this study.

1. For Inclusion Criteria, why is subtentorial hematoma (EDH) excluded?

Reply:

- 1) Thank you for your insightful remark. It is a really very important concern.
- 2) Compared to supratentorial EDH, subtentorial EDH showed variations in incidence, pathogenesis, surgical indications, and surgical technique et al. The distinct characteristics of subtentorial EDH may immensely increase the potential confounding and selection bias. So subtentorial EDH is excluded from our study.
- 3) Subtentorial EDH or posterior fossa extradural hematomas (PFEDH) are rare. The source of bleeding in most subtentorial EDH or PFEDH are venous. Sometimes bleeding is secondary from sigmoid sinus or transverse sinus injury. Indication for surgery of subtentorial EDH or PFEDH also reported in the studies published previously are the following: compression/obliteration of the cerebellar/perimesencephalic cisterns, compression/obliteration of the fourth ventricle, the presence

of hydrocephalus, marked compression to the brain in the supratentorial region, and hematoma thickness >15 mm. Moreover, most PFEDH patients were in a prone position with the head secured for surgery. The above and other characteristics not mentioned of subtentorial EDH are beyond the scope of our study.

- 4) However, as an important issue, we hope the relevant study of subtentorial EDH could be performed in the future.

2. As mentioned by the authors, most acute epidural hematomas do not require decompressive craniectomy. Is the removal of bone flap related to pupil dilation time? Postoperative cerebral infarction may also be preoperative hypotension, preoperative thrombus shedding.

Reply:

- 1) Thank you for your significant concern about factors associated with surgical removal of bone flap and potential risk factors for postoperative cerebral infarction secondary to AEDH.
- 2) In this study, removal of bone flap is not fully related to pupil dilation time. In this study, removing the bone flap is mainly related to elevated ICP and, possibly, increased brain swelling. Many clinical signs or symptoms could indicate raised ICP, and pupil dilation time is one of them. Relevant information will be collected in this study. We clarify indication for DC and the details for the surgical techniques in the **Treatment strategies** of **Methods and analysis** section. Please see **page 11** of the revised manuscript, **lines 14–19**, and **page 12, line 1-4**.
- 3) As for postoperative cerebral infarction risk factors, data of preoperative hypotension and thrombus are collected. We also collect potential information as possible confounding bias, such as preoperative imaging examination, the hematoma location, volume, the largest thickness and midline shift, basal cisterns compression, preoperative GCS score, and vital signs in a different time, and intraoperative ICP, et al., in our CRFs and protocol. We now reported accordingly in the **Potential bias and data analysis** of **Methods and analysis** section.

3. This research is time-consuming and involves a lot of staff. How to control the quality of the research. For example, neurosurgeons in different hospitals have different surgical skills and different opinions on whether bone flaps need to be removed during surgery. These all affect the results of the research. In addition, in China, for emergency surgical treatment of AEDH, neurosurgeons are junior doctors, how to ensure the quality of surgical treatment.

Reply:

- 1) Thank you for your sincere concern.
- 2) Control the quality of the research is an inevitable challenge for the most multicenter observational CER studies and certainly in ours. To control the quality, the study will establish a data management committee to supervise data quality. Clinical research associates (CRA) will regularly visit each participating center to strictly follow all program contents. This study holds a summary meeting every six months to discuss and solve research questions and outcome measures informed by patients' priorities, experiences, and preferences. In addition, our target will be to record detailed, informative management data on a standardized data collection form to address potential bias. We reported accordingly in the **Methods and analysis** section.
- 3) For surgery, firstly, the operation will be performed by a qualified neurosurgeon or neurosurgical resident in this study. Secondly, although the specific details of the operations may differ between surgeons or centers, the surgical techniques for evacuating AEDH are well established in China. Related international or Chinese surgical management guidelines have been published. Finally, detailed, informative management data are recorded on a standardized data collection form to address potential bias.

Reviewer: 3

Dr. Tsegazeab Laeke, Addis Ababa University

Comments to the Author:

It is an elaborate manuscript. I have however some points to raise. One of the points is that for AEDH patients the primary treatment modality is craniotomy. DC is only done when the patient has infarction as a result of brain herniation not for AEDH. And intra cerebral hemorrhage and infarction are the exclusion criteria for the study. It will be better if you describe what the customary indication for DC is for AEDH and the details for the surgical techniques.

Reply:

- 1) Thank you for your sincere suggestion. We appreciate your encouragement and the specific suggestions for improving this study.
- 2) We have reported indication for DC and the details for the surgical techniques accordingly in the **Treatment strategies** of **Methods and analysis** section. Please see **page 11** of the revised manuscript, **lines 12–19**, and **page 12, line 1-4**.

Reviewer: 4

Dr. Charles Hayfron-Benjamin, University of Ghana Medical School, Korle Bu Teaching Hospital

Comments to the Author:

COMMENTS

Yang et al. present a multicenter, prospective, and observational real-world study protocol aimed at evaluating different surgical treatment options for acute epidural hematoma. This proposed study is important and has the potential to fill important gaps in the public literature on the surgical management of acute epidural hematoma. The comparative effectiveness research design is appropriate for comparing the two forms of active surgical treatment for acute epidural hematoma. However, I have some comments and recommendations.

Reply:

Thank you for your positive comment on this study. We appreciate your encouragement and the specific suggestions for improving this study.

1. There are language/grammar errors in some portions of the manuscript. The authors should consider running the revised draft through a grammar checker. The tenses should also be appropriate/consistent; this is a protocol and the study is yet to be conducted.

Reply:

- 1) Thanks for your constructive suggestion.
- 2) We have carefully scrutinized the manuscript, and made corresponding revisions including some typos, grammatical errors and long sentences.

2. There are some discrepancies between the protocol published on ClinicalTrials.gov (NCT 04229966) and the current manuscript (protocol) draft. For example in the current draft, the age range in the eligibility criteria is 18 to 65 years. Under the recruitment information on ClinicalTrials.gov, the stated age range is ≥ 16 years. While revisions may be acceptable, they should be clarified/justified, especially as you refer to the trial registration in the protocol, and mentioned that the protocol has already been approved by the ethics committee/institutional review board of Renji Hospital.

Reply:

- 1) Thank you for your sincere suggestion.
- 2) We made adjustments accordingly.

3. The authors should clarify how they will address bias in the comparative effectiveness study design.

Reply:

- 1) Thank you for your sincere suggestion.
- 2) We made adjustments accordingly in the **Potential bias and data analysis** of **Methods and analysis** section. Please see **page 16** of the revised manuscript, **lines 1–19**. We now clarify how relevant distinct covariate information collection and statistical analyses are to control the potential selection, confounding, and information bias.

4. The methods section may benefit from a sentence/paragraph indicating the current status of the study. Authors should also consider rephrasing “Patients recruitment will start in April 2021...” to reflect the fact that this was an anticipated start time.

Reply:

- 1) Thank you for your sincere suggestion.
- 2) We made adjustments accordingly.

5. When a participant withdraws consent or decides to quit from the trial (especially those who had surrogates/legal representatives consenting on their behalf), will information previously collected be included in the analyses?

Reply:

- 1) Thank you for your sincere suggestion.
- 2) It's really a very important concern. Information previously collected of withdrawal will be included in the analyses. Before informed consent signed, the patient was informed that patients will be able to withdraw from the study at any point, but all data collected up to the point of drop out, including withdrawal, will be retained for use within analyses to adequately control selection bias. We made adjustments accordingly in the **Ethics and dissemination** section. Please see **page 19** of the revised manuscript, **lines 2–6**.

6. Conspicuously missing in the discussion section is the limitations of this study, including the study design.

Reply:

- 1) Thank you for your suggestion.
- 2) We made adjustments accordingly in the **Limitation of Methods and analysis** section. Please see **page 15** of the revised manuscript, **lines 12–18**.

7. Non-standard abbreviations should be defined on first use (e.g. ICP)

Reply:

- 1) Thanks for your suggestion.
- 2) We made adjustments accordingly.

VERSION 2 – REVIEW

REVIEWER	Wang, Xuanchi University of Science and Technology of China
REVIEW RETURNED	07-Jan-2022
GENERAL COMMENTS	The author's reply has solved our questions
REVIEWER	Hayfron-Benjamin, Charles University of Ghana Medical School, Physiology
REVIEW RETURNED	31-Dec-2021

GENERAL COMMENTS	The authors have sufficiently addressed my comments. Congratulations!
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